I) SYNTHESIS OF FLEXIBLE HETEROAROTINOIDS FOR ANTI-CANCER ACTIVITY

II) METAL FREE SYNTHETIC APPROACHES TO BIOACTIVE COMPOUNDS

By

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Major Field: ORGANIC CHEMISTRY

Abstract: The first project of this work involved the synthesis flexible heteroarotinoids for anti-cancer activity. Flexible Heteroarotinoids (Flex-Hets) are a class of substituted di-aryl compounds that exhibit potent anti-cancer activity without toxicity. Previously, our group developed a sulfur containing heteroarotinoid S-Het-A2 (NSC 721689), exhibited promising activity against 62 different cancer cell lines at micromolar concentration with excellent differentiation between normal and cancer cells. The primary goal of this work is to improve the activity of the lead compound S-Het-A2. To achieve this, we synthesized 42 modified heteroarotinoids and they were tested against human A2780 ovarian cancer cell line.

- Altering the linker unit: The thiourea unit in S-Het-A2 was replaced by acrylamide, *N*-benzylacetamide and thiazoline. Nitro- substitution on the ring B aryl group caused similar activity compared to S-Het-A2 for acrylamide linker. When *N*-benzylacetamide and thiazoline were used as linker, the compounds were completely devoid of activity.
- Nitrogen containing heteroarotinoids: The sulfur atom in the cyclohexyl ring in S-Het-A2 was replaced by nitrogen. Nitrogen heteroarotinods with a carbonyl group at C3 of ring A exhibited greater activity than the S-Het-A2, whereas a hydroxyl at C3 and Flex-Hets without a *gem*-dimethyl next to nitrogen atom trimmed the activity to a large extent.
- Tethering bioactive motifs to S-Het-A2 rings: A fragment based approach was attempted by joining ring A and ring B of S-Het-A2 with bioactive compounds such as indole, quinoline, oxazoline, furfuryl and aspirin. None of these compounds exhibited even moderate activity. However, reducing the nitro group of S-Het-A2 to an amino group resulted in enhanced acivity.

The second part of this work involved devising new methods for preparing biologically active compounds under metal free conditions. These methods are summarized below

- Synthesis of isoquinolinones, naphthyridinones pyrazoloquinazolinones, pyrazolopyridopyrimid-inones and benzimidazoquinazolinones have been developed using an *N*-acylation - S_NAr reaction sequence. The newly developed methods afforded better yields under milder reaction conditions compared to earlier reported methods.
- The S_NAr strategy was further extended to add enolates and amines to electron deficient vinylarenes. This method allowed enolates to add across unsubstituted and α-substituted electron deficient vinyl arenes.
- An efficient, inexpensive approach to synthesis 1,3,4-oxadiazole was established using catalytic NH_4Cl and also an efficient tandem reaction was designed to synthesize 4-chromanone using 20 mol% of bismuth(III) triflate.

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CHAPTER I

SYNTHESIS OF FLEXIBLE HETEROATORINOIDS FOR ANTI-CANCER ACTIVITY

1.1 Introduction:

Ovarian cancer is the most lethal gynecological malignancy and represents 3% of all female cancers with 239,000 new cases detected per year and 152,000 deaths per year worldwide.[1] In the United States alone, the detection rate for ovarian cancer is nearly 22,000 per year, with over 14,000 deaths reported annually.[2] The disease is also termed as the 'silent killer', as more than 80% of patients exhibit no symptoms if it is limited within the ovaries.[3] Over the last two decades, the 20% of patients diagnosed with early stage ovarian cancer had a five-year survival rate of over 90%.[3] Although more effective surgery as well as treatment with optimized combinations of cytotoxic drugs have improved the survival rate over the past five years, the overall cure rate remains only at 30%.[4] Thus there is a great demand to develop new agents to treat ovarian cancer and our research group has worked to combat this deadly disease by developing a new class of compounds called heteroarotinoids.

Heteroarotinoids are a family of synthetic compounds with a heteroatom in the arotinoid structure (arotinoids are the poly-aromatic analogues of retinoic acid). The basic structural units of heteroarotinoids **1** are designed to mimic the anticancer activity of *trans*-retinoic acid (**2**).[5] Biological studies of **2,** and related compounds, revealed that they possess high toxicity which limits their potential as a chemotherapeutic agents.[6] The high toxicity of **2** is thought to derive from its oxidation to metabolites **3** – **6**.[6] Strategic placement of a heteroatom at C4 in **2** could avoid the oxidation at this position, which leads to toxic metabolites **4** and **5**.[5] This strategy has been validated, and further addition of the benzene ring fused across C5 and C6 of the cyclohexyl

and incorporating C1' and C2' of the pendent chain in **1** would also prevent epoxidation, and thereby avoid formation of **3** from **2**.[5, 7-8] These successful outcomes resulted in coining the new term heteroarotinoids **1** where they possess an aryl ring fused to a saturated five- or six-membered ring containing a heteroatom (ring A) linked to another aromatic ring[9] (ring B) as shown in structure **1** (Figure 1.1).

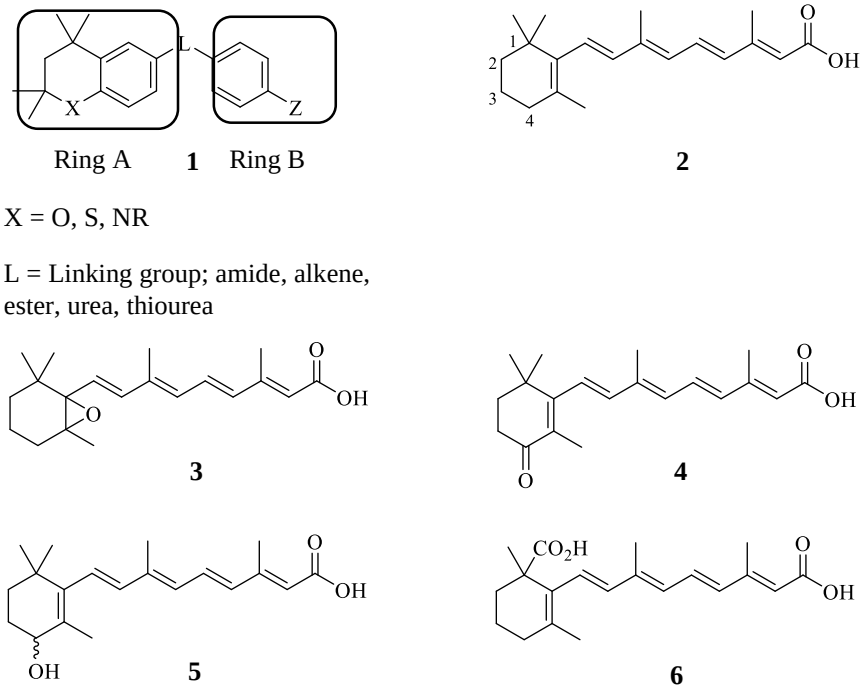


Figure 1.1. Basic structure of heteroarotinoids and retinoic acid and their toxic metabolites.

Intensive studies on the modification of heteroarotinoids have been reported involving the insertion of different linker fragments (L in **1**) to connect the two aryl rings. Structures with two atom linkers such as an amide (**9**), an alkene (**10**), an ester (**11**) or an *N*-methoxyamide (**12**), have been synthesized. Structures with three-atom linkers, such as propenone as in (**13**), propanol as in (**14**), and α-hydroxyamide as in (**15**) have also been prepared. The 1,4-diketone **16**, as a four-atom linker, has also been reported (Figure 1.2). All of these heteroarotinoids have shown potent anticancer activity with low toxicity.[10-13]

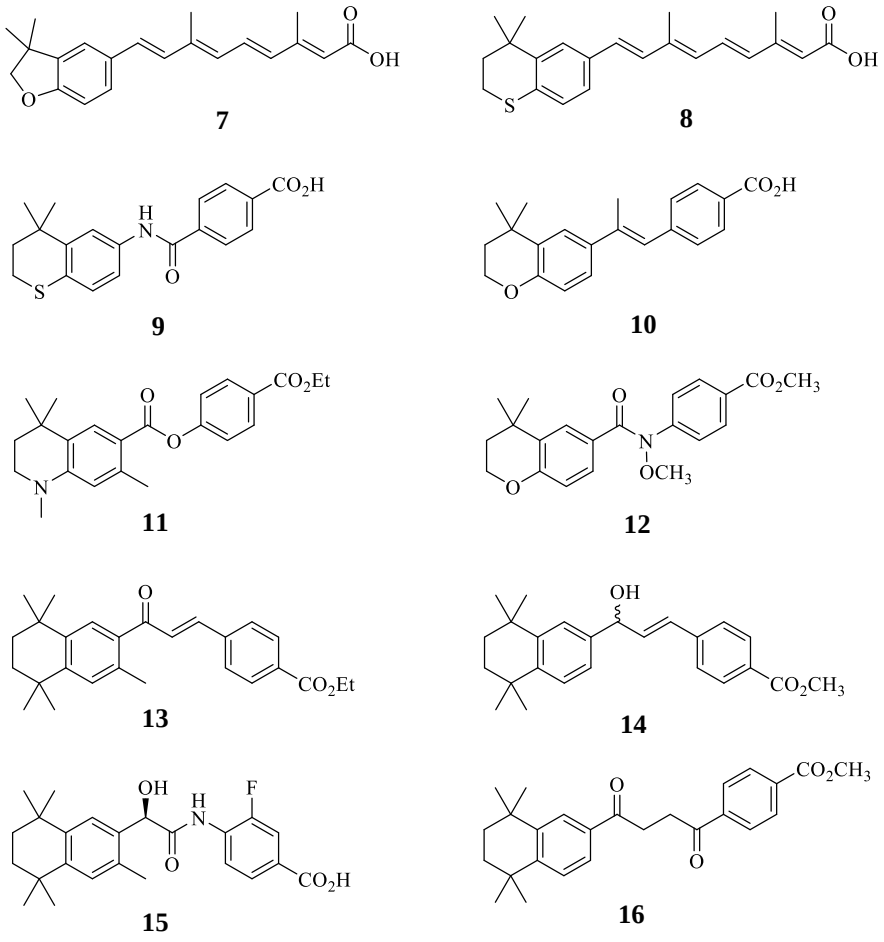


Figure 1.2. Heteroarotinoids with different atom linkers.

Flexible Heteroarotinoids (Flex-Hets) are heteroarotinoids compounds with three or more atom linkers. Incorporation of a more flexible linker between the aryl groups provides more degrees of freedom that can increase the binding affinity of the compound with the receptor. Derivatives incorporating a number of urea and thiourea linkers between the aryl groups have been investigated (Figure 1.3) and their increased flexibility resulted in a marked increase in activity of the compound.[11, 14] These Flex-Hets have potential anticancer activity against various kinds of cancer cells. Of all the Flex-Hets prepared to date, a derivative with a sulfur in the fused heterocycle of ring A linked by a thiourea group to ring B bearing a nitro group at C4, named as S-Het-A2 (**19**) exhibited the most promising activity on 62 different cancer cell lines.[15] Furthermore, S-Het-A2 exerted inhibitory activity on cancer cells, with excellent differentiation

between normal and cancer cells.[17] It also exhibited no mutagenicity, carcinogenicity, teratogenicity or toxicity and displayed a wide therapeutic window which suggested that its major metabolites were non-toxic.[11, 15-21]

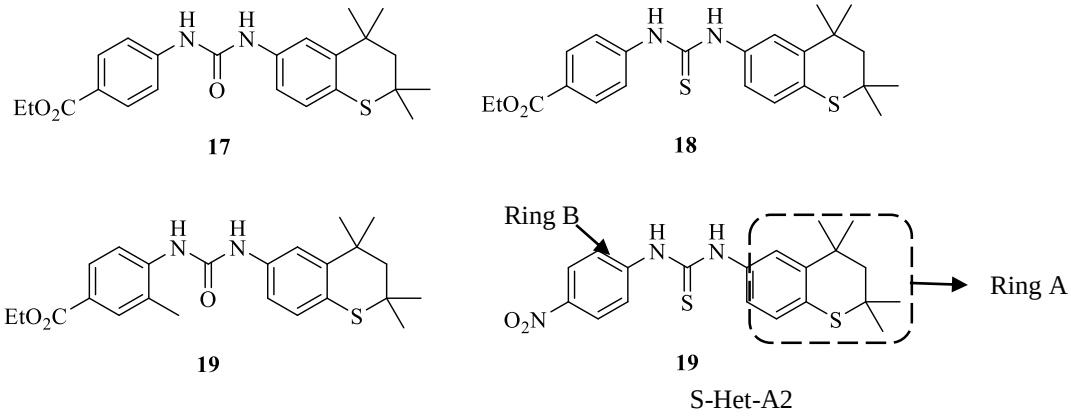


Figure 1.3. Examples of heteroarotinoids with three atom linker

Recently, S-Het-A2 has been approved for phase 0 clinical trials and these studies are in progress. However, we were interested in improving the activity of S-Het-A2, and as a part of our continuing effort, this work involved synthesizing a new class of Flex-Hets with the following changes:

1) altering the linker unit of S-Het-A2; 2) synthesizing nitrogen analogues of S-Het-A2; and

3) tethering bioactive molecules to S-Het-A2 rings.

1.2 Altering the linker unit of S-Het-A2

1.2.1 Increasing the linker unit using acrylamide.

Modifications to the linker units have been envisioned in S-Het-A2 and other Flex-Hets to enhance the activity and reduce the toxicity.[22-26] It was noted that altering the linker units resulted in a marked increase in inhibitory activity from **21** to **23** (Figure 1.4). These compounds revealed the relationship between the linker and its anticancer activity. Recent progress by the Gurkan group demonstrated that structure **21**, which contains an acrylamide linker,[27] enhanced the biological activity of the compounds in a related synthetic retinoid family. Based on molecular

modeling, we had previously predicted that allowing certain flexibility within the ring system of the molecule could specifically increase the H-bonding capabilities between the ligands and the binding pocket of the retinoic acid receptors.[11] We found that structures with 3-atom linkers exhibited improved anti-cancer activity compared to 2-atom linkers presumably due, in part, to the increased flexibility of the molecule. Recently, two retinoid derivatives containing 4-atom linkers, as in compound **23**, have been reported.[27-28]

Building on these observations, we hypothesized that selected compounds with 4-atom linkers would possess increased flexibility and increased conjugation with the aromatic ring B, which might improve the efficacy of S-Het-A2. We subsequently designed and synthesized a new series of 11 compounds incorporating a cinnamamide linked to a sulfur containing heterocycle (ring A). This modification was projected to enhance the biological activity of the related S-Het-A2 system and would, hopefully, reduce the toxicity of these synthetic, modified retinoids. We now report the synthesis and the biological activity of these 4-atom linked second-generation Flex-Hets against the ovarian cancer cell line A2780.[29] These new heteroarotinoids then were appraised relative to S-Het-A2.

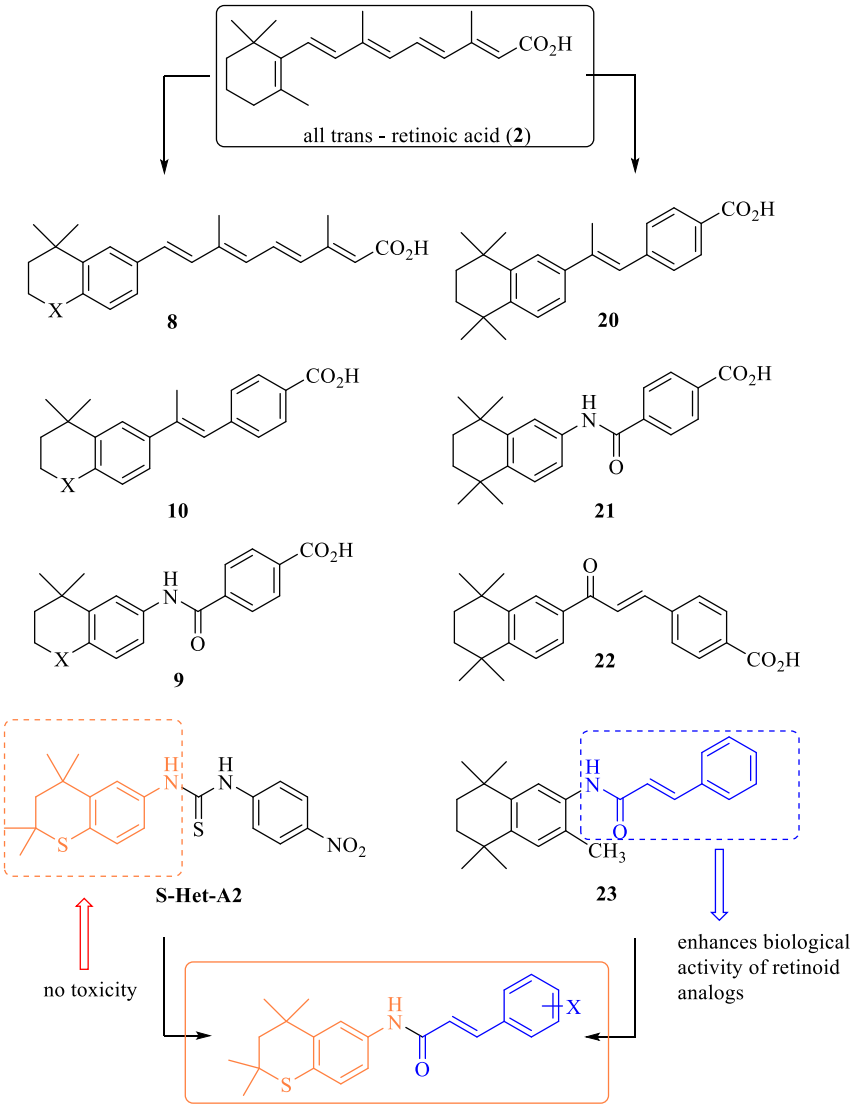
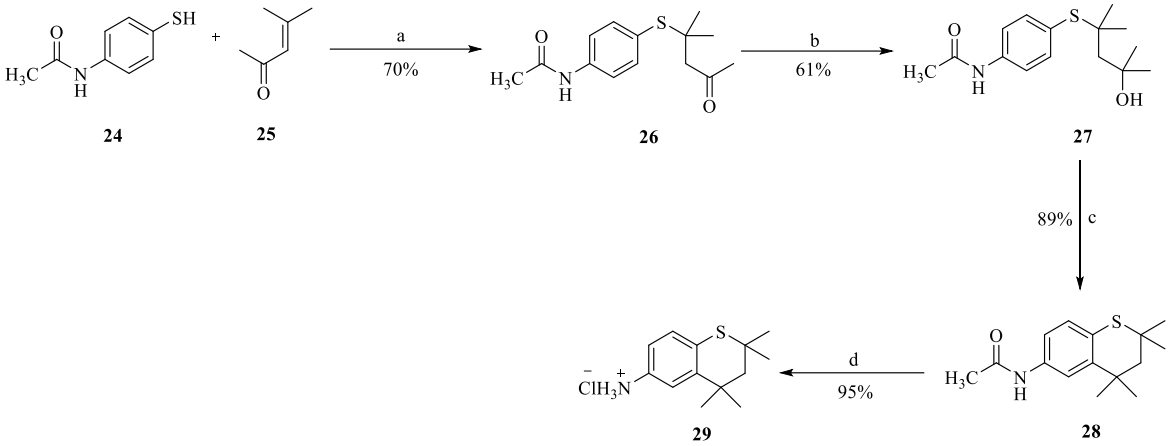


Figure 1.4. Rationale for designing Flex-Hets with an acrylamide linker.

1.2.2 Results and Discussion for increasing the linker unit using acrylamide

The syntheses of cinnamide-linked Flex-Het analogues required 5-7 steps. Initially, 4-acetamidothiophenol (**24)** was treated with mesityl oxide (**25)** in the presence of triethylamine (Scheme 1.1). A two-fold excess of mesityl oxide and base was required to perform this Michael reaction to afford the ketone product **26** in 70% yield.[30] Notably, this Michael addition gave higher yields only when the reactants were added portion-wise. A standard, one-time addition gave the products in lower yields, along with recovered excess starting materials.

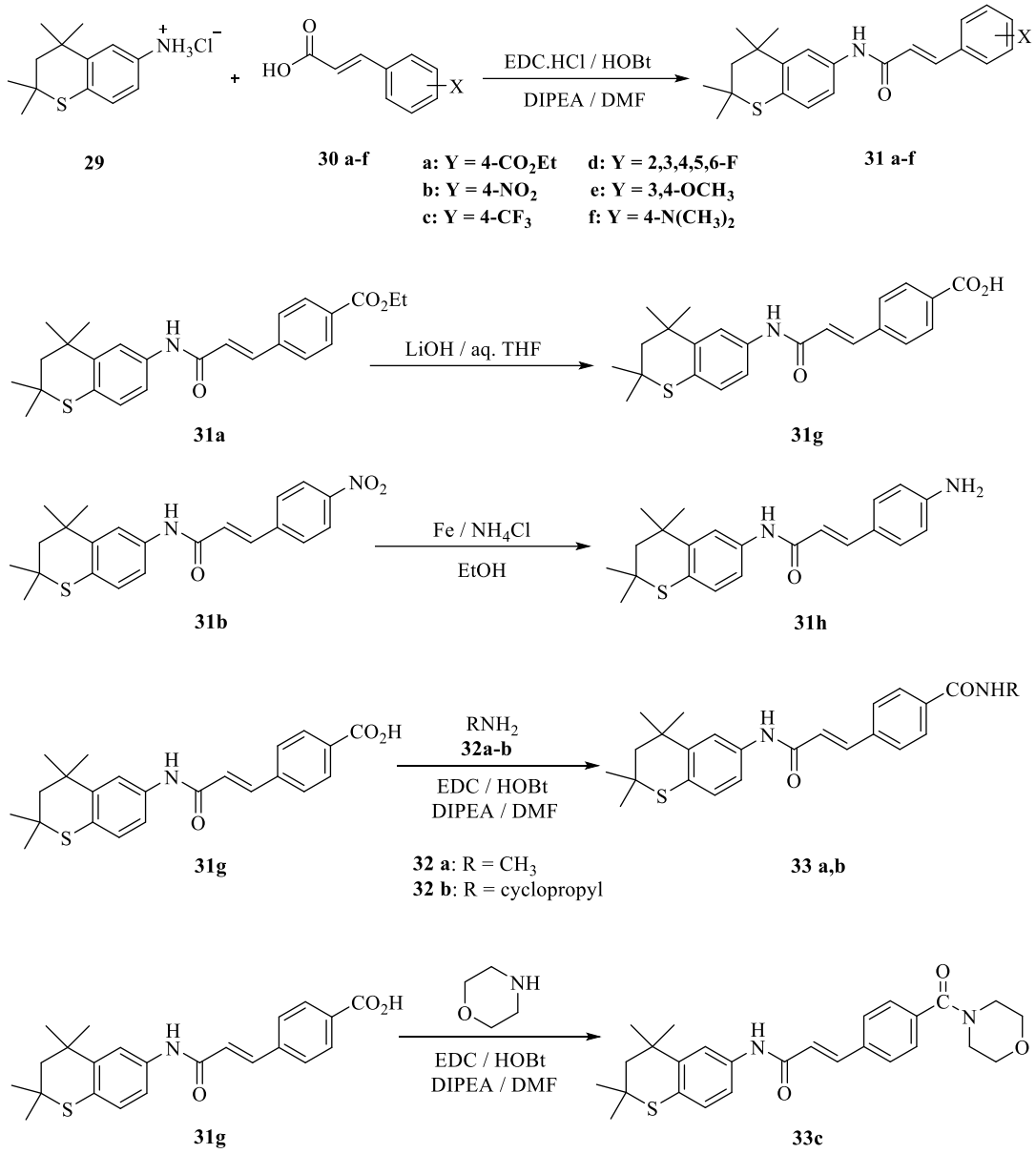


a) TEA, $CHCl_3$, reflux 24 h; b) CH_3Li, THF, -50 ^oC; c) $AlCl_3$, chlorobenzene, 80 ^oC; d) 6 M HCl, MeOH

Scheme 1.1. Synthesis of intermediate **29**

Subsequent addition of methyllithium to **26** at -50 ^oC led to the formation of tertiary alcohol **27**. Even in this reaction, the sequence of reactant addition played a critical role in the outcome. When the substrate was dissolved in tetrahydrofuran, followed by dropwise addition of methyllithium, a low conversion was observed, and product purification was difficult. With inverse addition, however, the reaction afforded a cleaner conversion of **26** to **27**, and the purification process was simplified. Dehydration-cyclization of **27** by the action of $AlCl_3$ in chlorobenzene generated the desired thiochroman derivative **28** in 89% yield. Refluxing **28** with 6 M HCl in methanol furnished the desired aminothiochroman in 95% yield as its hydrochloride salt **29**.

Aminothiochroman **29** was joined with cinnamic acid derivatives **30a-f** using a standard coupling promoted by 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDC.HCl), hydroxy-benzotriazole (HOBt), and diisopropylethylamine (DIPEA) to generate the desired cinnamamides **31a-f** (Scheme 1.2). The 4-carboxycinnamamide derivative **31g** was prepared by saponifica- tion of **31a** using lithium hydroxide in aqueous tetrahydrofuran.



Scheme 1.2. Synthesis of Flex-Hets **31a-h** and **33a-c**

The 4-aminocinnamamide congener **31h** was realized by reduction of the corresponding 4-nitro derivative **31b** using iron/ammonium chloride in ethanol. Furthermore, the acid **31g** was converted to amides **33a-c**, as illustrated (Scheme 1.2), using the standard coupling protocol. In order to anchor our spectral assignments, an X-ray structure determination was conducted for **31a**. With the exception of the fused tetrahydrothiopyran moiety, the perspective view of **31a**

(Figure 1.5) shows a nearly planar structure with good conjugation of the two aromatic rings with the acrylamide linker.

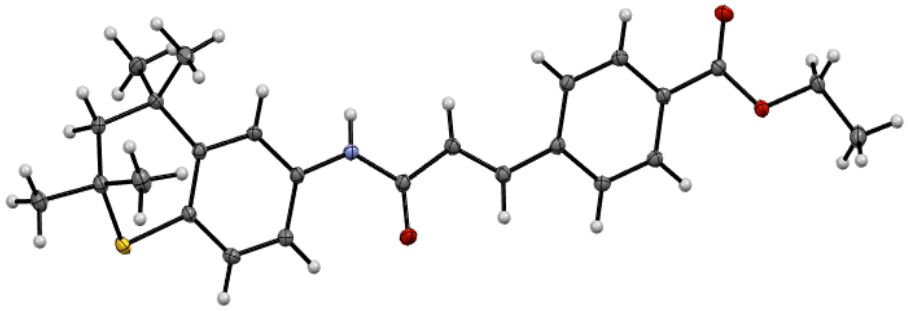
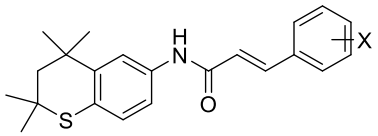


Figure 1.5. X-ray structure of **31a**

These Flex-Hets were screened to identify structural features important for cancer cell inhibition activity. S-Het-A2 was used as a standard for comparison. The biological effects of the compounds were assessed using a cytotoxicity assay on the human A2780 ovarian cancer cell line (Table 1.1). The three most active compounds **31b**, **31f** and **33c** contained a nitro, a tertiary amino and an oxomorpholino group, respectively, as the ring B aryl substituent (Table 1.1). Compound **31b**, with a nitro substituent as in S-Het-A2, exhibited activity comparable to S-Het-A2. Replacement of the nitro substituent with a dimethylamino group (**31f**) reduced the efficacy, but not the potency. The oxomorpholino substituent (**33c**) slightly reduced the potency and efficacy. The efficacy and potency were reduced to a greater extent when the substituent was an amino group (**31h**), a methylamide group (**33a**), or the related cyclopropylamide group (**33b**). Compounds lacking a nitrogen atom at the para position of ring B exhibited potencies similar to S-Het-A2, but with 60 - 70% reduced efficacy (Table 1.1). The ethyl ester derivative **31a** had only 43% efficacy compared to S-Het-A2, although the former was slightly more potent. Previous comparison of S-Het-A2 with the ethyl ester derivative S-Het-A3 (CO_2Et in place of NO_2) did not demonstrate improved potency in the context of thiourea linker containing compounds.[31]

Table 1.1. The activity data of Flex-Hets **31a-h** and **33a-c**



Compound	X	Potency IC_{50} (μM)	Efficacy (% SHetA2)	Maximal Activity (% Growth Inhibition)
Non-Nitrogen-Substituted Flex-Hets				
(SHetA2)	4-NO_2	2.98 ± 0.10	100	93.17 ± 2.37
31a	4-CO_2Et	1.49 ± 0.13	43.19 ± 5.01	40.37 ± 4.88
31c	4-CF_3	1.09 ± 0.22	30.73 ± 8.65	28.61 ± 7.66
31d	2,3,4,5,6-F	5.42 ± 0.36	31.16 ± 5.26	29.17 ± 5.33
31e	3,4-OCH_3	7.81 ± 0.23	37.07 ± 12.18	34.73 ± 11.44
31g	4-CO_2H	>1000	0	0
Nitrogen-Substituted Flex-Hets				
31b	4-NO_2	2.17 ± 1.69	97.29 ± 10.75	85.07 ± 4.10
31f	4-N(CH_3)$_2$	2.42 ± 0.14	71.33 ± 7.34	68.02 ± 10.27
31h	4-NH_2	5.18 ± 0.23	49.65 ± 0.34	52.02 ± 9.63
33a	4-*N*-methylamide	5.04 ± 0.46	52.22 ± 5.00	47.67 ± 5.48
33b	4-*N*-cyclopropylamide	5.52 ± 0.58	67.35 ± 5.50	45.11 ± 10.05
33c	4-oxomorpholino	4.64 ± 0.24	89.32 ± 0.35	77.47 ± 1.11

Interestingly, the related carboxylic acid derivative **31g** was completely devoid of activity. The CF_3 derivative **31c** was about 30% as effective as S-Het-A2, but had a *ca.* three-fold higher potency. Compound **31d**, which possessed a perfluorophenyl, was also about 30% as effective as S-Het-A2, and it had an almost two-fold reduced potency. The dimethoxy compound **31e** exhibited 37% efficacy relative to S-Het-A2 and a *ca.* five-fold attenuated potency. The study

demonstrated that various substitutions at the para position on the aryl moiety had highly variable effects on the anticancer activity of Flex-Hets. Compound **31b** (X = NO_2), which was identical to S-Het-A2 except for the linker group, had similar but slightly reduced potency and efficacy, indicating the importance of the nitro group. The oxomorpholino derivative **33c** was less potent than S-Het-A2, but the efficacy was only 10% lower than that of S-Het-A2. Other substitutions containing nitrogen atoms exhibited similar reduced activity, while substitutions lacking nitrogen atoms were the weakest, and the carboxyl group abolished activity. Recent studies revealed that S-Het-A2 binds to and disrupts protein interaction with mortalin.[16, 32]

An overall appraisal of the four best derivatives **31b**, **31f**, **33b**, and **33c** revealed that a para electron donating group (**31f**-NH_2) and several para electron withdrawing groups (**31b**-NO_2; **33b**-(CO)-cyclopropylamino; **33c**-C(O)-morpholino) exhibited reasonable efficacy within the experimental limits, although potency varied within less than a two-fold range. Compounds with the two larger para groups (**33b** and **33c**) had reduced potency compared to **31b** and **31f** and may reflect steric hindrance. All four of these compounds have polar components, and, thus, there is not a simple rationale for the observed activity.

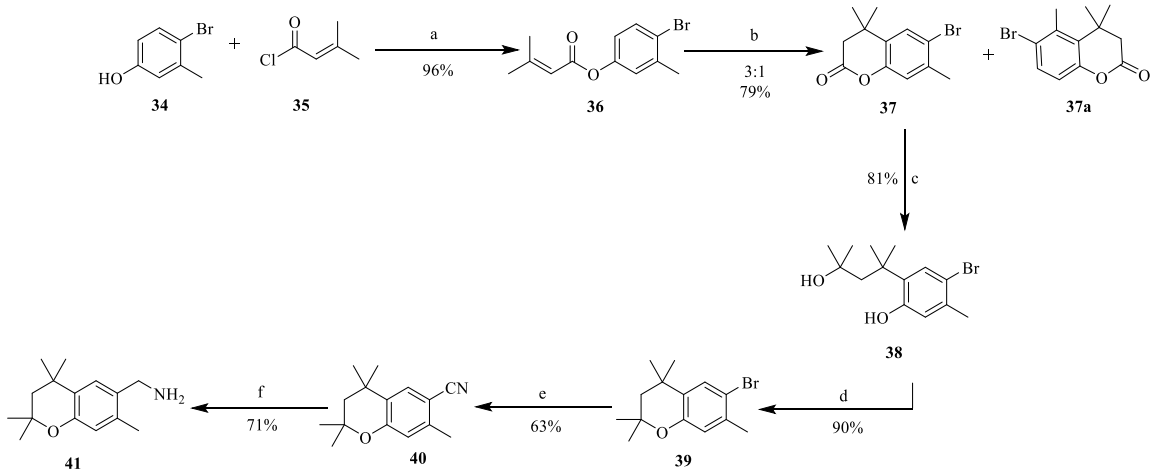
1.2.3 Altering the linker unit using *N*-benzylacetamide.

Based on the input from our collaborator (for *N*-benzylacetamide).

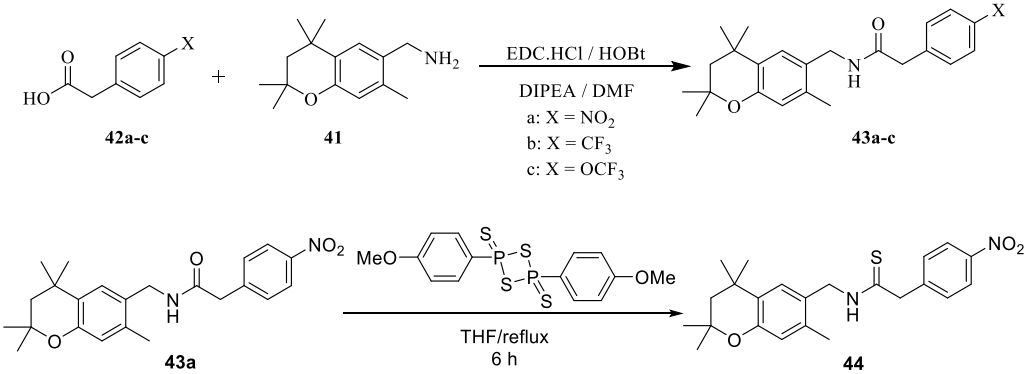
1.2.4 Results and Discussion for altering the linker unit *N*-benzylacetamide

The syntheses of Flex-Hets **43a-c** and **44** required 7–8 steps with the first 4 steps following the reported procedure.[33] Treating 4-bromo-3-methylphenol (**34**) with sodium hydride in tetrahydrofuran and reacting with dimethylacryloyl chloride (**35**) in tetrahydrofuran at 0 ^{o}C, and warming to room temperature (Scheme 1.3), afforded ester **36** in 96% yield. Treatment of **36** with aluminum chloride in dichloromethane at 0 ^{o}C and stirring at room temperature for 24 h provided ring-closed chromanone **37** and **37a** in a ratio of 3:1. Notably, running this reaction under ice-cold conditions for longer decreased the isomer ratio to 1:1. Therefore, the ice bath was removed

immediately after the addition was complete. The regioisomers were separated by column chromatography. Addition of methyllithium to **37** at 0 °C in ether, followed by stirring at room temperature for 48 h, gave an 81% yield of diol **38.** Dehydration-cyclization of **38** was achieved using concentrated phosphoric acid at 100 °C for 1 h to afford the 6-bromo-2,2,4,4-tetramethylchroaman (**39)** in nearly quantitative yield. Cyanation of **39** was performed using a modified Rosenmund-von Braun procedure wherein L-proline promoted the CuCN cyanation of the aryl bromide,[34-35] to afford **40** in 63% yield. Several milder reduction procedures, such as Kagan's reagent (SmI_2),[36] $NiCl_2.6H_2O$,[37] and $CoCl_2.6H_2O$[38] were attempted for the reduction of cyano compound **40**. Unfortunately, these methods failed on our system. Surprisingly, a clean conversion of **40** to **41** (71% yield) was observed using lithium aluminum hydride in refluxing tetrahydrofuran.



a) NaH/THF, 0 °C to rt; b) $AlCl_3$, 0 °C to rt, 24 h; c) MeLi/THF, 0 °C to rt, 48 h; d) H_3PO_4, 110 °C; e) CuCN, L-proline, DMF, 140 °C; f) LAH, THF, reflux

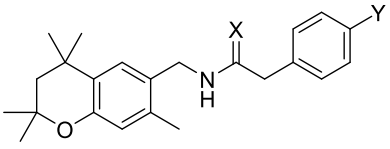


Scheme 1.3. Synthesis of Flex-Hets **43a-c** and **44**

Chroman **41** was condensed with phenylacetic acid (**42a-c**) derivatives using a standard coupling promoted by EDC.HCl, HOBt, and DIPEA to generate the desired *N*-benzylacetamides **43a-c** (Scheme 1.3). Thioamide **44** was obtained by treating **43a** with Lawesson's reagent at room temperature and then refluxing for 6 h to afford the thioamide **44** in 72% yield.

The biological activities of these Flex-Hets were assessed using a cytotoxicity assay on the human A2780 ovarian cancer cell line. Of these **4** compounds, the most active compound was **43c** containing a trifluoromethoxy with an acetamide linker. This compound retained nearly 70% of the activity of S-Het-A2 with a slight decline in potency (Table 1.2), whereas the trifluoromethyl derivative **43b** showed only 56% of the activity. Surprisingly, the nitro-substituted acetamide **43a**, and thioacetamide **44** were almost completely devoid of activity in the cytotoxic assay, in defiance of the modelling study predictions.

Table 1.2. Activity data for Flex-Hets **43a-c** and **44**

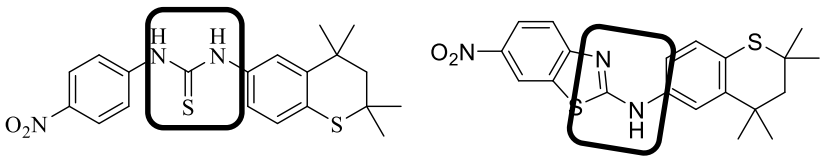


Compound	**X**	**Y**	**Potency IC_{50} (μM)**	**Efficacy (% SHetA2)**	**Maximal Activity (% Growth Inhibition)**
(SHetA2)			2.71	100	83.75
43a	4-NO_2	O	4.64	11.5	8.6

43b	4-CF_3	O	4.199	56.13001	47.0092
43c	4-OCF_3	O	4.644	79.55297	66.62607
44	4-NO_2	S	No fit	0	0

1.2.5 Altering the linker unit with a thiazoline ring

As has already been discussed, molecular modeling has predicted that allowing flexibility within the ring system of the molecule could specifically increase the H-bonding capabilities between the ligands and the binding pocket of retinoic acid receptors.[11] We found that structures with three-atom linkers exhibited improved anti-cancer activity compared to two-atom linkers, presumably due in part, to the increased flexibility of the molecule. However, there is a lack of evidence suggesting that flexibility is essential. Therefore, we sought to study the activity profile of S-Het-A2 by replacing the thiourea linker unit with a system that has the same elements but more restricted flexibility.



S-Het-A2 **45**

Figure 1.6. Structural comparison of S-Het-A2 and its modified compound **45** with a thiazoline instead of a thiourea

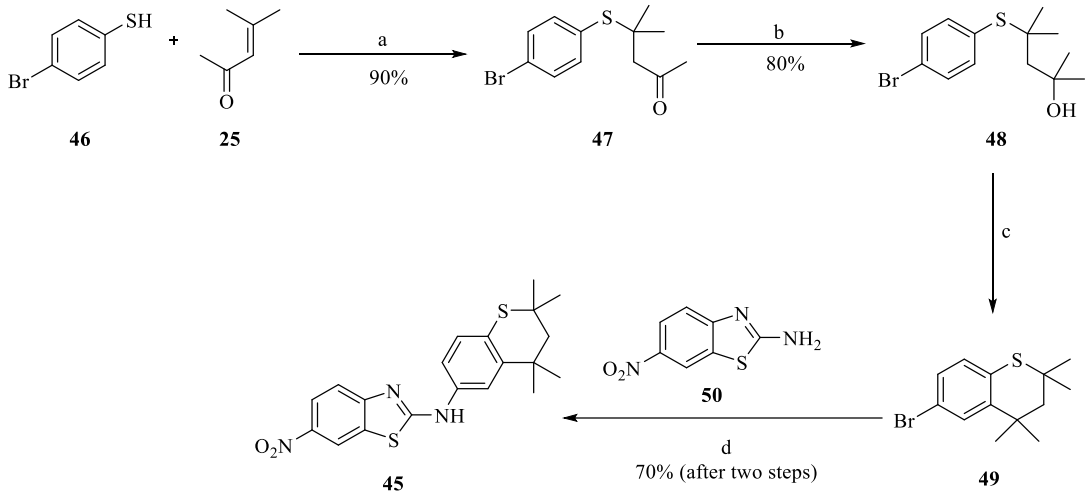
The amino-thiazoline ring system was chosen, because it has the necessary elements and also the same number and type of elements as in thiourea linker, and at the same time, it will restrict the flexibility since it is fused to the aryl ring. Moreover, thiazoline and its derivatives are well-known for their versatile pharmacological activity as antibiotics, radioprotectives, pheromones,

and metal chelators, as well as anticancer and anti-HIV agents.[39] Based on the above considerations, S-Het-A2 was modified as illustrated in Figure 1.6.

1.2.6 Results and discussion for altering the linker unit with the thiazoline ring

The synthesis of **45** was performed according to the synthetic procedure used to prepare the key intermediate **29**. Michael reaction of 4-bromobenzenethiol (**46**) with mesityl oxide (**25**) in the presence of triethylamine afforded ketone **47** in 90% yield. Addition of methyllithium to **47** at -50 ^{o}C provided the tertiary alcohol **48** in 80% yield. Subsequent treatment with aluminum chloride in refluxing dichloroethane afforded the thiochroman derivative **49**. This compound was used for the next step without further purification. Following the modified Ullmann reaction[40] and purification by column chromatography, **45** was isolated in 70% yield.

Assessing compound **45**, using a cytotoxicity assay on the human A2780 ovarian cancer cell line revealed that the compound lost its activity completely, confirming the importance of flexibility in the linker despite of the existence of the same elements.



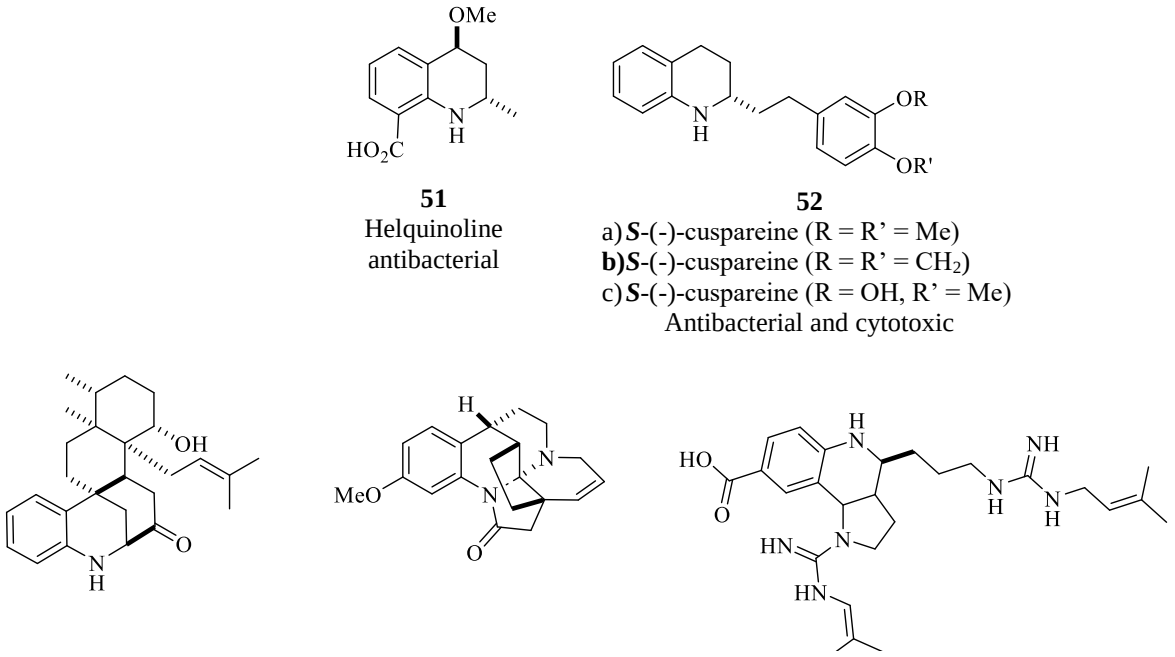
(a) TEA, $CHCl_3$, reflux 24 h; (b) CH_3Li, THF, -50 ^{o}C; (c) $AlCl_3$, dichloroethane, 80 ^{o}C; (d) CuI, L-proline, DMF, K_2CO_3, 140 ^{o}C

Scheme 1.4. Synthesis of thiazoline ring system **45**

1.3 Synthesizing nitrogen containing heteroarotinoids

Nitrogen heterocycles are among the most significant structural components of pharmaceuticals. A recent study reports that, out of 1994 pharmaceuticals approved by the U.S. FDA, 89% of them contain at least one nitrogen atom.[41] The study also reveals that at least 59% of unique small-molecule drugs contain a nitrogen heterocycle. These numbers are incredibly high percentages compared to sulfur (26%), fluorine (13%) or other heteroatoms. Surprisingly, the average number of nitrogen atoms per drug is 2.3 for all the small-molecule drugs, while it is 3.1 for those that contain a nitrogen heterocycle.[41]

As part of our ongoing effort to improve the activity of S-Het-A2, we sought to insert a nitrogen in place of sulfur or oxygen in ring A of the heteroarotinoid ring system to get a tetrahydroquinoline ring system. Tetrahydroquinolines are important structural motifs in many biologically active molecules. It is prevalent in many natural products and pharmaceutical products as well. Its prevalence in natural products can be substantiated with a few examples. Helquinoline (**51**) a relatively simple molecule with significant antibiotic properties. Similarly, cuspareine (**52a**) and related compounds **52b** and **52c** have shown antibacterial as well as cytotoxic activity. More complex systems include (+)-aspernomine (**53**), a potent cytotoxic agent, and (−)-isoschizogaline (**54**), a potentially useful antibiotic. Finally, (−)-martinellic acid (**55**) is known to be a non-peptide antagonist for the bradykinin B1 and B2 receptors (Figure 1.7).[42]



51
Helquinoline
antibacterial

52
a) ***S***-(-)-cuspareine (R = R' = Me)
b)*S*-(-)-cuspareine (R = R' = CH_2)
c) ***S***-(-)-cuspareine (R = OH, R' = Me)
Antibacterial and cytotoxic

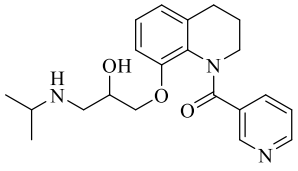
53
(+)-aspernomine
Cytotoxic

54
(-)-isoschizogaline
antibacterial

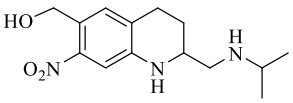
55
(-)-martinellic acid
Bradkykinin receptor antagonist

Figure 1.7. Natural products incorporating a tetrahydroquinoine moiety.

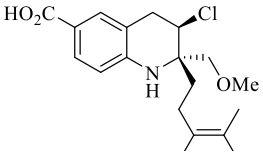
The 1,2,3,4-tetrahydroquinoline nucleus is prevalent in many synthetic pharmaceuticals, and it can be understood with the following examples. Nicainoprol (**56**) is an antiarrhythmic drug, oxamniquine (**57**) is a schistosomicide, and virantmycin (**58**) is an antiviral antibiotic that also possesses antifungal activity. Additionally, compound **59** is being evaluated for use in the treatment of HIV, and compound **60** is gathering attention as a means to slow the onset of Alzheimer's disease. Compound **61** is currently being evaluated as an antimalarial agent. Furthermore, compound **62** has demonstrated activity as a cholesterol ester transfer protein (CETP) inhibitor and would be useful for treating hypercholesterolipidemia, while L-689,560 (**63**) is a neuroprotective agent with potential to minimize ischemic nerve damage following a stroke or heart attack (Figure 1.8).[42]



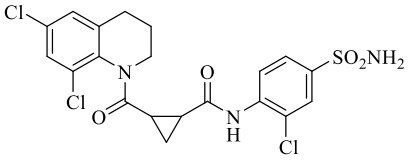
56
Nicainoprol
antiarrhythmic



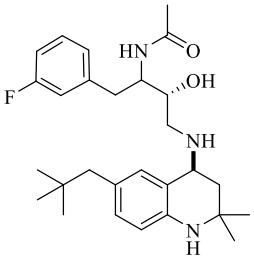
57
Oxamniquine
schistosomicide



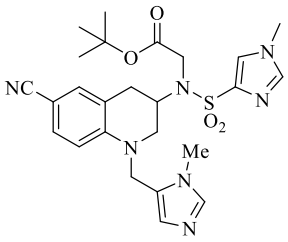
58
Viratmycin
antibiotic



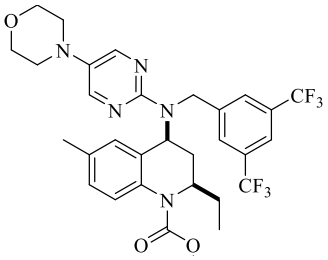
59 – Anti-HIV



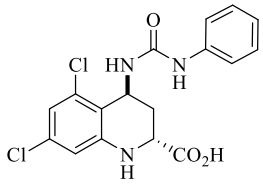
60 - Alzheimer's disease



61 – Anti-malarial



62 – CETP inhibitor



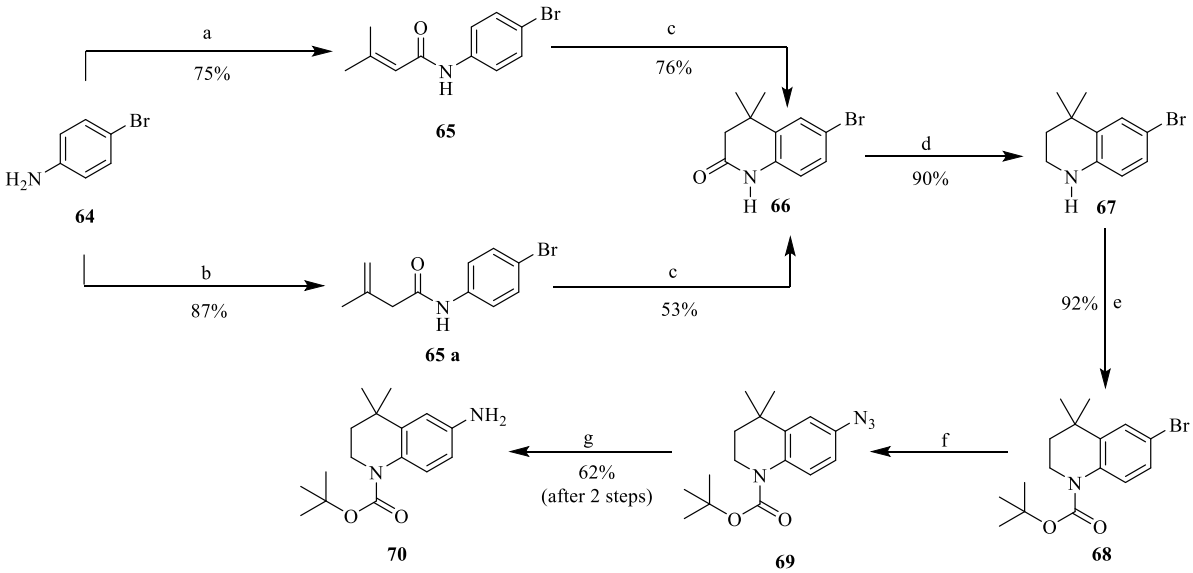
63 - Neuroprotectant

Figure 1.8. Examples of pharmaceuticals containing the tetrahydroquinoine moiety.

Based on the above facts and our earlier results with related heteroarotinoids, we assumed these new derivatives (with nitro, amino, trifluoromethyl and trifluoromethoxy groups) would have greater potential as anticancer agents with low toxicity. Additionally, we believed that the nitrogen atom had a greater ability to hydrogen bond, which could allow these new derivatives to easily fit into the binding pocket of the receptor. Furthermore, to overcome the solubility problem with heteroarotinoids containing sulfur or oxygen, these nitrogen containing heteroarotinoids would increase the hydrophilicity of the molecule thereby increasing the absorption and distribution of the drug in the blood stream and could be formulated as a salt.

1.3.1 Results and Discussion for synthesizing nitrogen containing heteroarotinoids

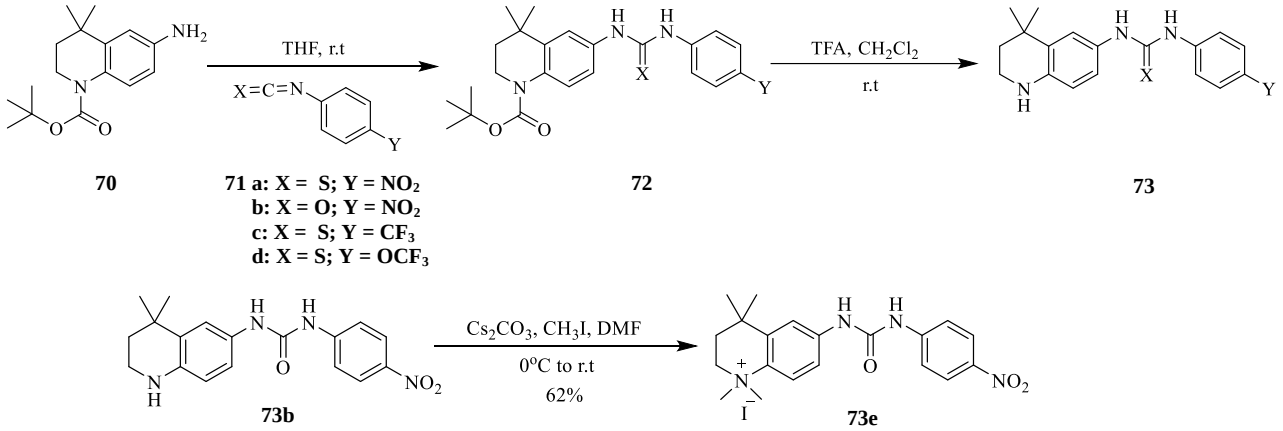
Nitrogen heteroarotinoids **73a-e** were prepared starting from 4-bromoaniline (**64**) and 3-methylbut-2-enoyl chloride (Scheme 1.5). Initially, treating a 1:1 ratio of 4-bromoaniline and 3-methylbut-2-enoyl chloride in the presence of triethylamine at 0 ^{o}C and stirring at room temperature for 18 h gave the non-conjugated amide **65a** in 87% yield. Although this method provided the amide **65a** in excellent yield, Friedel-Crafts reaction of this compound using 1.5 equivalent of aluminum chloride in refluxing dichloroethane gave only a moderate yield (53%) of **66**. We attempted to optimize the Friedel-crafts reaction by varying the solvent and molar ratio of aluminum chloride, hoping to increase the yield of **66.** Unfortunately, all our attempts failed and we planned to generate **65a**, in order to perform additional experiments to optimize Friedel-Crafts reaction. At this time, in an effort to reduce the reaction time of amidation, we treated 2.0 equivalent of 4-bromoaniline with an equivalent of 3-methylbut-2-enoyl chloride in refluxing chloroform. Interestingly, these conditions afforded the conjugated amide **65** exclusively (75%), and subjecting **65** to Friedel-Crafts reaction conditions with 1.5 equivalent of $AlCl_3$ gave a 76% yield of **66.**



a) 3-methylbut-2-enoyl chloride, $CHCl_3$, reflux, 5 h; b) 3-methylbut-2-enoyl chloride, TEA, 0 ^{o}C to rt, 18 h; c) $AlCl_3$, dichloroethane, 80 ^{o}C; d) BH_3-DMS, toluene, 0 ^{o}C to 110 ^{o}C; e) *n*-BuLi, Boc_2O, THF; f) NaN_3, DMF, L-proline, 140 ^{o}C; g) H_2, Pd/C, MeOH

Scheme 1.5. Synthesis of key intermediate **70**

The yield of **66**, after 2 steps, was greater with **65** than with **65a**. Hence, we followed this procedure to generate **65** on a gram scale. Treating **66** with borane-dimethylsulfide complex at 0 ^{o}C and refluxing for 3 h afforded **67** in 90% yield, and the resulting secondary amine was protected with Boc-anhydride using *n*-butyllithium. Conceivably, the Boc-group would not withstand the harsh reaction conditions for the direct conversion of aryl bromides to aryl amines using ammonium hydroxide,[40] we converted the aryl bromide to the aryl azide using an L-proline promoted, CuI-catalyzed coupling Ullmann-type reaction to generate **69**.[43] The azide compound **69** was then subjected to Pd/C catalyzed hydrogenation to afford the key intermediate amine **70** in 62% yield after two steps.



70 **71 a: X = S; Y = NO_2** **72** **73**
b: X = O; Y = NO_2
c: X = S; Y = CF_3
d: X = S; Y = OCF_3

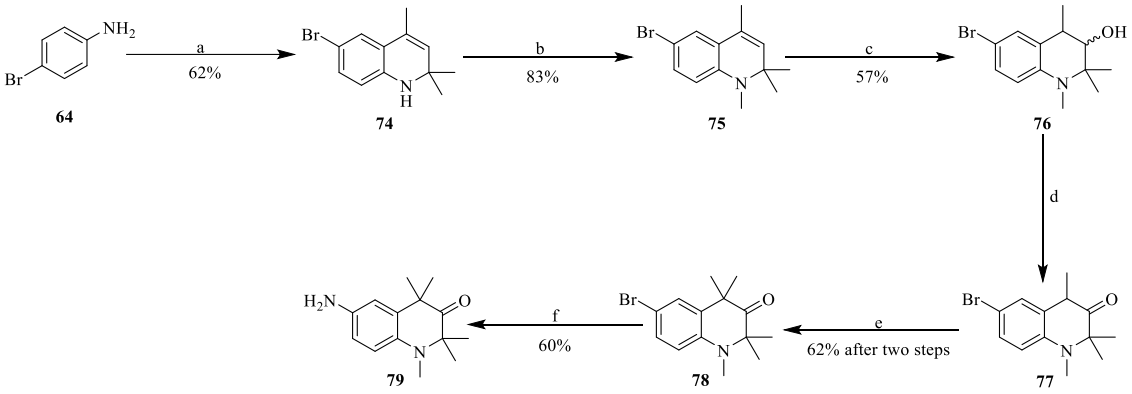
73b **73e**

Scheme 1.6. Synthesis of nitrogen heteroarotinoids **73a-e**

The aryl amine **70** was added to aryl iso(thio)cyanates **71a-d** (Scheme 1.6) in tetrahydrofuran at room temperature to afford the Boc-protected (thio)urea compounds **72a-d**, and this was followed by secondary amine deprotection using trifluoroacetic acid in dichloromethane. The pure compounds **73a-d** were obtained in excellent yield (83–92%) by acid-base workup and crystallization from a mixture of pentane/ether. The quarternary ammonium salt **73e** was obtained

in 62% yield, by reacting **73b** with methyl iodide using cesium carbonate in a sealed tube at room temperature for 24 h.

The another series of nitrogen heteroarotinoids outlined in Schemes 1.7 and 1.8 were also prepared starting from 4-bromoaniline (**64**) in 7–8 steps. Dihydroquinoline **74** was prepared in 62% yield by the Skraup reaction of acetone with 4-bromoaniline (**64**)[44] using bismuth(III) trifluoromethane- sulfonate (reflux, 3d). Attempts were made to reduce the reaction time and improve the yield using other reagents and methods such as scandium triflate,[45] zirconium chloride, ceric ammonium nitrate[47] and Amberlyst 15 as well as microwave assisted synthesis of dihydroquinoline using indium trichloride.[46] These approaches however, resulted in lower yields as well as longer reaction times.



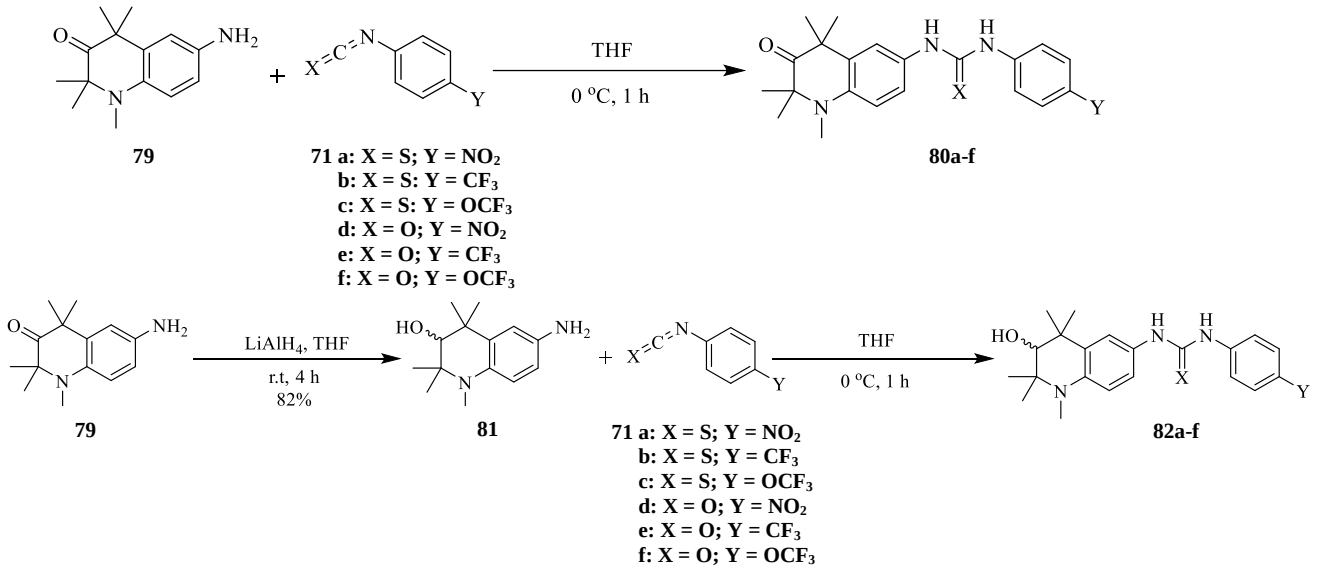
a) acetone, $Bi(OTf)_3$, reflux, 3d; b) NaH, CH_3I, DMF, r.t. 24 h; c) BH_3-THF complex, THF, 10 – 15°C; 3M NaOH, 30% H_2O_2 d) $(COCl)_2$, DMSO, TEA, CH_2Cl_2, 0 – 5 °C; e) LiHMDS, CH_3I, THF; f) CuI, L-proline, aq.NH_3, DMF

Scheme 1.7. Synthesis of tetrahydroquinolinone **79**

Methylation of the secondary amine in **74** using sodium hydride and methyl iodide in dimethylformamide, followed by hydroboration of the conjugated double bond provided alcohol **76** in 57% yield.[48] The hydroxyl group was oxidized by the Swern procedure to generate quinolinone **77** and this was used without purification for the next step. Notably, the chlorosulfonium ion generated using oxalyl chloride and DMSO should be added dropwise to a solution of **76** in dichloromethane at -78 °C. Addition of **76** to the generated sulfonium ion resulted in very poor yield of ketone **77**. The tetramethyl ketone **78** was obtained by generating

the enolate of **77** using LiHMDS followed by dropwise addition of methyl iodide in tetrahydofuran. The aryl amine **79** was obtained by modified Ullmann reaction condition[40] as described above.

The hindered ketoaniline **79** was added to iso(thio)cyanate **71(a-f)** in tetrahydrofuran at room temperature to generate nitrogen containing heteroarotinoids **80(a-f)** (Scheme 1.8). Compounds **82(a-f)** were obtained by reduction of **79** using lithium aluminium hydride and treating the resultant alcohol **81** with iso(thio)cyanates **71(a-f)**.

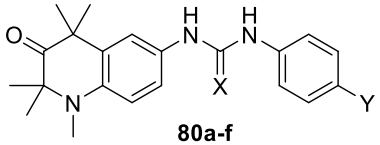


Scheme 1.8. Synthesis of nitrogen heteroarotinoids **80a-f** and **82a-f**

These compounds were all tested using a cytotoxicity assay against the human ovarian cancer cell line A2780. Of these, 17 compounds (**73a-e, 80a-f, 82a-f**), compounds **80a**, **80b**, **80d, 80e** and **80f** exhibited better activity compared to the standard compound S-Het-A2. The potency and efficacy of **80e** and **80f** were reasonably higher than that observed for S-Het-A2. On the other hand, the derivatives having the nitro substituent with the urea linker **80d** and the thiourea linker **80a,** and the trifluoromethyl subtituent **80b** showed an increase in efficacy and a slight decline in

potency, compared to S-Het-A2. Their increase in activity can be attributed to the presence of the carbonyl functional group at C3, which increases the hydrogen bonding to the receptor.

Table 1.3. Activity data for Flex-Hets **80a-f**



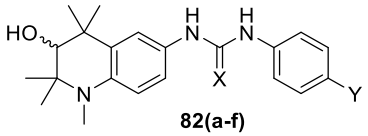
80a-f

Compound	**X**	**Y**	**Potency IC_{50} (µM)**	**Efficacy (% SHetA2)**	**Maximal Activity (% Growth Inhibition)**
(SHetA2)			2.71	100	83.75
80a	NO_2	S	5.099	102.4907	83.40909
80b	CF_3	S	3.344	105.2334	85.6411
80c	OCF_3	S	3.376	46.97892	39.34511
80d	NO_2	O	4.096	105.4367	88.30383
80e	CF_3	O	2.641	103.1104	86.3557
80f	OCF_3	O	2.495	102.0376	85.45706

Compounds **82(a-f)** containing a hydroxyl group at the C3 of ring A, are expected to have improved activity because the hydroxyl group, together with the ring nitrogen should increase the hydrogen bonding ability and the hydrophilicity of the compound, thereby increasing the solubility. Unfortunately, all of these compounds (**82a-f**) exhibited no inhibitory activity against

the human ovarian cancer cell line A2780. These findings lead one to draw the conclusion that ring A, can accommodate a neutral functional group like a carbonyl as in compound **80(a-f)** and retain the moderate activity. Compound **82a**, with a close resemblance to S-Het-A2 but with a hydroxyl group at C3 and an *N*-methyl instead of sulfur lost its activity completely. This observation anchors our conclusions about these compounds.

Table 1.4. Activity data for Flex-Hets **82a-f**

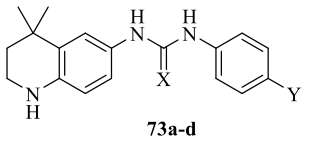


82(a-f)

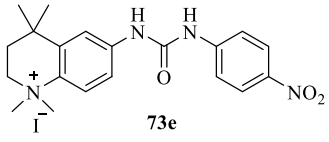
Compound	X	Y	Potency IC_{50} (μM)	Efficacy (% SHetA2)	Maximal Activity (% Growth Inhibition)
(SHetA2)			2.71	100	83.75
82a	NO_2	S	6.343	20.65407	16.80871
82b	CF_3	S	7.852	19.93126	16.22047
82c	OCF_3	S	5.172	21.08904	17.1627
82d	NO_2	O	6.156	13.84531	11.26761
82e	CF_3	O	20	9.146878	7.660562
82f	OCF_3	O	7.829	18.33266	14.9195

Compounds **73a-e**, without a *gem*-dimethyl next to a nitrogen atom, was also devoid of activity. None of these compounds exhibited even moderate activity against the human ovarian cancer cell line A2780, signifying the importance of the *gem*-dimethyl group next to a heteroatom. Compound **73e**, a quarternary ammonium compound, inhibiting only 12% of the cancer cell line.

Table 1.5. Activity data for Flex-Hets **73a-e**



73a-d



73e

Compound	X	Y	Potency IC_{50} (μM)	Efficacy (% SHetA2)	Maximal Activity (% Growth Inhibition)
(SHetA2)			2.71	100	83.75
73a	NO_2	S	3.3	11.9	9.04
73b	CF_3	S	5.2	41.77	31.83
73c	OCF_3	S	>200	NA	NA
73d	NO_2	O	>200	NA	NA
73e			2.4	15.49	11.78

1.4 Tethering bioactive molecules to S-Het-A2 rings.

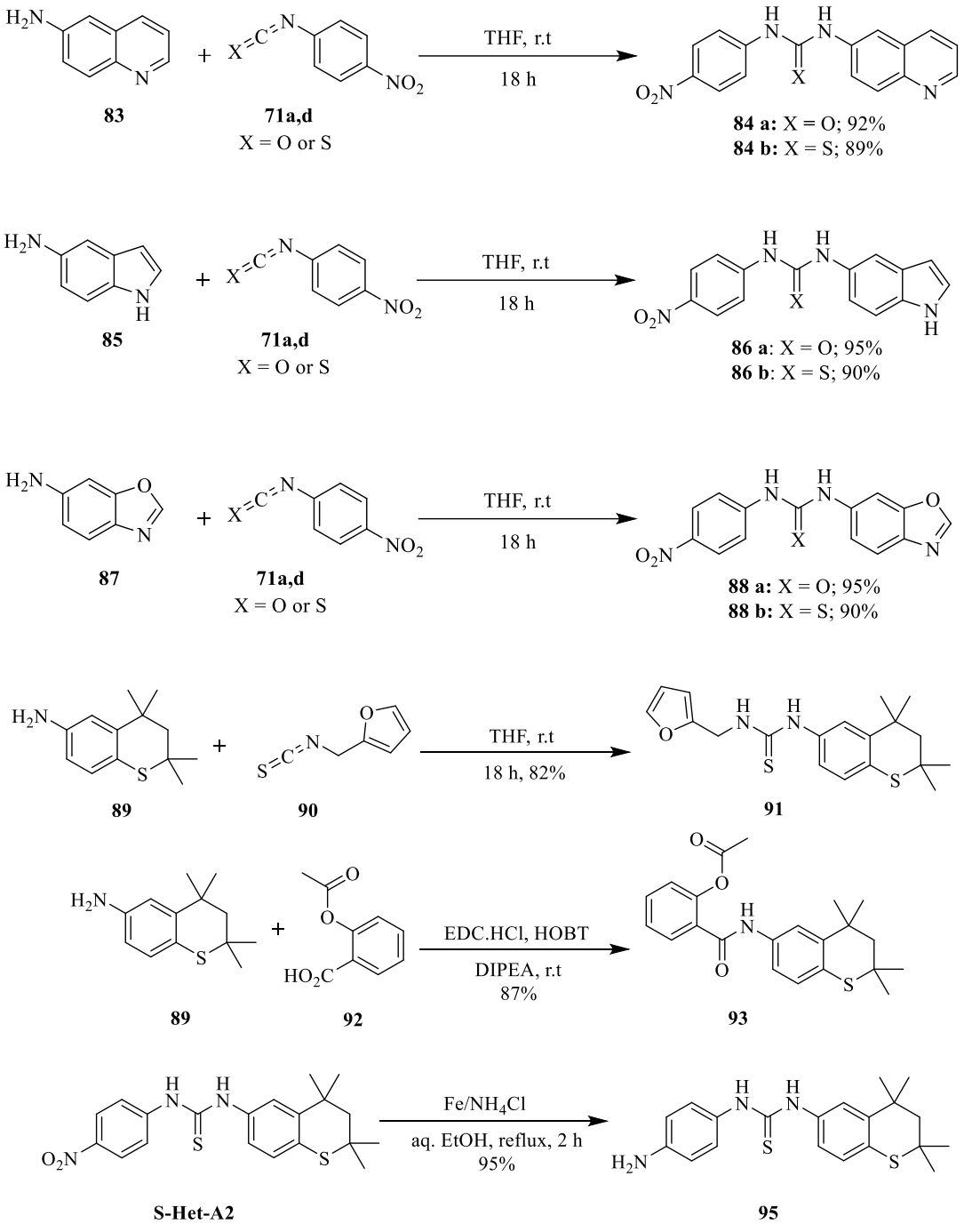
Our common approach to improve the activity of our lead compound S-Het-A2 involved systematic changes of ring A, such as replacing sulfur by nitrogen or oxygen and increasing the length of the linker unit. Though these efforts have given convincing results, the time, the effort and cost of these systematic changes are enormous. As a part of this work, we sought to change our lead compound by tethering the ring A or ring B to known bioactive molecules such as quinolone, oxazole, indole, furfuryl, and 2-acetylsalicyl derivatives. Amino derivatives of quinolone, oxazole, indole are commercially available and hence condensing with thiocyanates or

isothicyanates to install ring B were achieved easily, thereby reducing the cost and time. It also allowed us to assess the activity of these compounds at a faster rate. The same explanation holds for the furfuryl and acetyl salicylic acid compound, because furfuryl isothocyanates and acetyl salicylic acid are commercially available. Hence, it could be condensed with ring A of S-Het-A2 readily.

The current approach is similar to fragment based drug discovery, in which a large number of bioactive molecules would be screened against known protein targets.[49] This method is efficient for identifying fragments (hit molecules) quickly. Further buildup of the fragments would then help to identify a lead compound.[49] However, in our case, we designed our lead compound, and the current effort is to improve its activity further.

1.4.1 Results and discussion for tethering bioactive molecules to S-Het-A2 rings

Compounds **84(a,b)**, **86(a,b)** and **88(a,b)** were obtained by reacting the corresponding (Scheme 1.9) amino compound with 4-nitrophenyl isocyanate **71d** or its isothiocyanate **71a**. Compound **91** was obtained in 82% yield by treating **89** with 2-(isothiocyanatomethyl)furan **90**. Structure **93** was obtained in 87% yield by acid-amine coupling of **92** and **89**. Finally drug candidate **95** was prepared by treating S-Het-A2 with iron powder and ammonium chloride in ethanol at 82 ^{o}C. The reaction mass was filtered through Celite® and passed through a silica gel column in order to ensure complete removal of metal impurities.



Scheme 1.9. Tethering of bioactive motifs to ring A or ring B of S-Het-A2

These 9 compounds were assessed by cytotoxic assay against the human ovarian cancer cell line A2780 and it revealed that amino compound **95** is the most active compound (Table 1.7), because

its potency and efficacy were slightly greater than the standard compound S-Het-A2. The remaining compounds were inactive.

Table 1.6. Activity data for bioactive compounds tethered to S-Het-A2 rings.

Compound	Potency IC_{50} (μM)	Efficacy (% S-Het-A2)	Maximal Activity (% Growth Inhibition)
(SHetA2)	2.71	100	83.75
84a	>50	NIL	NIL
84b	8.3	31.70	24.68
86a	6.02	NIL	NIL
86b	2.5	NIL	NIL
88a	4.9	NIL	NIL
88b	>50	NIL	NIL
91	>50	NIL	NIL
93	6.02	NIL	NIL
95	2.4	104.67	81.42

1.5 Conclusion

In summary, we have synthesized 42 heteroarotiniods in an effort to improve the activity of our lead compound S-Het-A2 and these were assessed using cytotoxic assay against the human ovarian cancer cell line A2780.

1.5.1 Altering the linker unit of S-Het-A2

In this study, we developed a new route to synthesize Flex-Hets with an acrylamide linker (**31a-h, 33a-c**), an *N*-benzylacetamide linker (**43a-c and 44**) and a compound with a thiazoline ring linker (**45)**. These compounds were evaluated for biological activity against the human A2780 ovarian cancer cell line. Changing from a 3-atom linker to a 4-atom linker resulted in a range of

activities. Compound **31b** with a NO_2 substituent, and an acrylamide linker displayed comparable activity to that of our lead compound S-Het-A2. On the other hand, compounds **43a** and **44** with a nitro substituents and *N*-benzylacetamide and thioacetamide linkers, respectively, were completely devoid of activity, which explains the importance of the thiourea linker. The importance of thiourea unit was further justified by compound **45**, which was completely inactive due to lack of flexibility in thiazoline ring system.

1.5.2 Synthesizing nitrogen containing heteroarotinoids

In an effort to improve the activity of S-Het-A2, 17 nitrogen heterarotinoids were synthesized and tested. Of these nitrogen heteroarotinoids, compounds with a keto at C3 exhibited good activity against the human ovarian cancer cell line A2780. Compounds that are significantly better than S-Het-A2 are **80b**, **80d-f**. Compound **80b** with a CF_3 substituent and a thiourea linker and compound **80d** with a nitro substituent and a urea linker exhibited a slight increase in potency and efficacy compared to S-Het-A2. While compounds **80e** and **80f** possessing the urea linker unit with CF_3 and OCF_3 substituents exhibited greater potency and efficacy. However, nitrogen heteroarotinoids with a hydroxyl group and without a *gem*-dimethyl next to the nitrogen atom were completely devoid of activity.

1.5.3 Tethering bioactive molecules to S-Het-A2 rings

Finally, an approach similar to fragment based drug discovery allowed us to access and assess the acitivity of nine heteroarotinoids, that were prepared by tethering bioactive molecules like quinolone, indole, oxazole, furfuryl and acetylsalicylic acid to the S-Het-A2 A or B ring. Unfortunately, eight of these compounds proved completely devoid of activity. Surprisingly, reducing the nitro group of S-Het-A2 to an amino group furnished compound **95** with the highest potency and efficacy of all compounds.

1.6 Chemistry

1.6.1 Increasing the linker unit using acrylamide

General methods: Commercial anhydrous *N*,*N*-dimethylformamide was stored under dry N_2 and transferred by syringe into reactions when needed. Tetrahydrofuran was dried over potassium hydroxide pellets and distilled from lithium aluminum hydride prior to use. All other commercial reagents and solvents were used as received. Unless otherwise indicated, all reactions were carried out under dry N_2 in oven-dried glassware. Reactions were monitored by thin layer chromatography (TLC, Analtech No 21521) using silica gel GF plates. Preparative separations were performed by column chromatography on silica gel (Davisil®, grade 62, 60 - 200 mesh) containing UV-active phosphor (Sorbent Technologies No UV-05) slurry packed into quartz columns. Band elution for all chromatographic separations was monitored using a hand-held UV lamp. Melting points were uncorrected. IR spectra were run as chloroform solutions on NaCl disks. The ^{1}H- and ^{13}C-NMR spectra were measured in the indicated solvent at 400 MHz and 100 MHz, respectively, using tetramethylsilane as the internal standard with coupling constants (*J*) given in Hz.

***N*-{4-[(2-Methyl-4-oxopentan-2-yl)thio]phenyl}acetamide** (**26**). To a stirred solution of acetamidothiophenol (**24**) (25.0 g, 149.7 mmol) in dry chloroform (200 mL) was added triethylamine (21.0 mL, 149.7 mmol), followed by addition of mesityl oxide (**25**) (17.0 mL, 149.7 mmol). The resulting slurry was heated to reflux (bath temperature 70 °C). Two additional portions of triethylamine (10.5 mL, 74.5 mmol) and mesityl oxide (8.6 mL, 74.5 mmol) were added at regular intervals of 4 h, and the resulting solution was refluxed for 16 h after the final addition. The resulting reaction mixture was cooled, filtered through Celite® and washed with chloroform (2 x 50 mL). The combined organic layers were washed with water (2 x 100 mL), saturated aqueous NaCl, dried ($MgSO_4$), and concentrated under vacuum to give a yellow oil.

The crude reaction mixture was then purified by silica gel column chromatography and eluted with dichloromethane:ethyl acetate (1:1) to afford **26** (27.8 g, 70%) as a pale yellow solid, mp 49-51 °C. IR: 3310, 1699, 1676 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.90 (br s,1H), 7.53 (d, 1H, *J* = 8.8 Hz,

2H), 7.45 (d, *J* = 8.8 Hz, 2H), 2.65 (s, 2H), 2.19 (s, 3H), 2.15 (s, 3H), 1.36 (s, 6H); ^{13}C NMR ($CDCl_3$): δ 206.9, 168.6, 139.0, 138.3, 126.2, 119.6, 54.3, 47.0, 32.1, 28.0, 24.5.

***N*-{4-[(4-Hydroxy-2,4-dimethylpentan-2-yl)thio]phenyl}acetamide (27**). To a stirred solution of methyllithium in ether (198 mL, 316.5 mmol, 1.6 M) in tetrahydrofuran (300 mL) at -50 ºC was added dropwise **26** (28 g, 105.5 mmol) in tetrahydrofuran (200 mL) over 30 - 45 min. The reaction mixture formed a white precipitate, which was slowly warmed to room temperature over a period of 3 h. Finally, the mixture was stirred at room temperature for 1 h. The reaction mass was then cooled to 0 ºC, and the mixture was quenched by dropwise addition to ice water (150 mL). After adjusting the solution to pH 6-7 by addition of 6 M aqueous HCl, the solution was extracted with ethyl acetate (2 x 250 mL). The combined organic extracts were washed with saturated aqueous NaCl (1 x 150 mL), dried ($MgSO_4$), and concentrated under vacuum to afford a dark brown liquid. To the crude mixture was added chloroform (60 mL) with cooling to 0 ºC for 1 h, which afforded a yellow solid. The solid was then filtered and dried under vacuum to afford **27** (18 g, 61%) as a pale yellow solid, mp 141-142 ºC. IR: 3400, 3303, 1676 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.68 (br, s, 1H), 7.52 (m, 4H), 3.50 (br s, 1H), 2.19 (s, 3H), 1.77 (s, 2H), 1.34 (s, 6H), 1.33 (s, 6H); ^{13}C NMR ($CDCl_3$): δ 168.4, 138.8, 138.1, 126.3, 119.6, 72.0, 52.0, 49.2, 32.2, 30.8, 24.6.

***N*-(2,2,4,4-Tetramethylthiochroman-6-yl)acetamide** (**28**). To a stirred solution of **27** (18 g, 63.9 mmol) in chlorobenzene (125 mL) at room temperature was added portion-wise anhydrous aluminum chloride (10.22 g, 76.7 mmol) over a period of 45 min, and reaction mixture was refluxed for 90 min. The reaction mixture was cooled to room temperature and quenched with ice cold water (150 mL) to give a thick suspension. The solid was removed by filtration through Celite® and washed with ethyl acetate (2 x 100 mL). The layers were separated, and the aqueous layer was extracted with additional ethyl acetate (2 x 100 mL). The combined organic extracts were washed with saturated aqueous NaCl, dried ($MgSO_4$), and concentrated under vacuum to

give a crude yellow oil. The crude product was purified on a silica gel column using hexanes:ethyl acetate (1:1) to afford the product **28** (15.0 g, 89%) as a pale yellow solid, mp 105-107 ºC. IR: 3295, 1662 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.60 (br s, 1H), 7.27 (d, *J* = 2.3 Hz, 1H), 7.20 (dd, *J* = 8.2, 2.3 Hz, 1H), 7.04 (d, *J* = 8.2 Hz, 1H), 2.16 (s, 3H), 1.92 (s, 2H), 1.39 (s, 6H), 1.35 (s, 6H); ^{13}C NMR ($CDCl_3$): δ 168.3, 143.4, 135.1, 128.4, 128.2, 118.7, 118.2, 54.4, 42.0, 35.7, 32.4, 31.4, 24.4.

2,2,4,4-Tetramethylthiochroman-6-amine hydrochloride (**29**). To a stirred solution of **28** (15.0 g, 56.9 mmol) in methanol (75 mL) was added 6 M aqueous HCl (75 mL). The reaction mixture was heated to 90 ºC for 1 h, followed by cooling to room temperature. The reaction was concentrated to 1/4 of its initial volume. The resulting crude mixture was cooled to 0 ºC and maintained at this temperature for 1 h to yield a solid. This material was filtered and dried under vacuum to afford **29** as a white solid (14.0 g, 95%), mp 208-209 ºC. IR: 2922, 2853 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 10.08 (s, 2H), 7.48 (s, 1H), 7.22 (d, *J* = 8.3 Hz, 1H), 7.09 (d, *J* = 8.3 Hz, 1H), 1.94 (s, 2H), 1.42 (s, 6H), 1.40 (s, 6H); ^{13}C NMR (DMSO-d_6): δ 144.2, 132.0, 130.0, 129.1, 122.0, 121.2, 53.5, 42.6, 35.8, 32.6, 31.6.

General procedure for synthesizing cinnamamides (31a-f). To a stirred solution of each cinnamic acid **30a-f** (0.5 mmol) in *N*,*N*-dimethylformamide (5 mL) was added diisopropylethylamine (1.5 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (0.55 mmol), and 1-hydroxylbenzotriazole (0.55 mmol). After stirring for 1 h at room temperature, 2,2,4,4-tetramethyl-6-aminothiochroman hydrochloride (**16**, 0.55 mmol) was added. The resulting mixture was stirred at room temperature for 12 h. The reaction mixture was poured into ice (approx. 100 g) and was stirred for 30 min. The aqueous layer was then extracted with ethyl acetate (3 x 100 mL). The combined organic layers were washed with saturated aqueous NaCl (2 x 50 mL), dried ($MgSO_4$), and concentrated under vacuum to afford the corresponding crude cinnamamide

derivatives. The compounds were further purified by silica gel column chromatography and eluted with hexanes:ethyl acetate (1:1) to afford the pure cinnamamides **31a-f**.

Ethyl-4-{3-Oxo-3-[(2,2,4,4-tetramethylthiochroman-6-yl)amino]prop-1-en-1-yl}benzoate (**31a**). Yield: 195 mg (0.46 mmol, 92%) as a white solid, mp 184-185 ^{o}C; IR: 3288, 1716, 1646 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 8.05 (d, *J* = 8.2 Hz, 2H), 7.80 (br s, 1H), 7.78 (d, *J* = 15.4 Hz, 1H), 7.58 (m, 1H), 7.55 (d, *J* = 8.2 Hz, 2H), 7.30 (m, 1H), 7.10 (d, *J* = 8.4 Hz, 1H), 6.66 (d, *J* = 15.6 Hz, 1H), 4.39 (q, *J* = 7.0 Hz, 2H), 1.95 (s, 2H), 1.41 (s, 6H), 1.40 (t, 3H, *J* = 7.0 Hz), 1.40 (s, 6H); ^{13}C NMR ($CDCl_3$): δ 166.1, 163.2, 143.7, 140.9, 138.9, 135.1, 131.4, 130.1, 128.8, 128.6, 127.7, 123.1, 118.7, 118.1, 61.2, 54.4, 42.2, 35.8, 32.5, 31.6, 14.3. Anal. Calcd for $C_{25}H_{29}NO_3S$: C, 70.89; H, 6.90; N, 3.31. Found: C, 70.71; H, 6.76, N, 3.30.

3-(4-Nitrophenyl)-*N*-(2,2,4,4-tetramethylthiochroman-6-yl)acrylamide (**31b**). Yield: 188 mg (0.48 mmol, 95%) as a yellow solid, mp 212-213 ^{o}C; IR: 3281, 1662, 1521, 1340 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 10.3 (s, 1H), 8.30 (d, *J* = 8.8 Hz, 2H), 7.89 (d, *J* = 8.8 Hz, 2H), 7.80 (d, *J* = 2.0 Hz, 1H), 7.70 (d, *J* = 15.8 Hz, 1H), 7.51 (dd, *J* = 8.4, 2.1 Hz, 1H), 7.05 (d, *J* = 8.4 Hz, 1H), 6.98 (d, *J* = 15.8 Hz, 1H), 1.92 (s, 2H), 1.37 (s, 6H), 1.35 (s, 6H); ^{13}C NMR (DMSO-d_6): δ 165.4, 143.5, 140.5, 139.5, 138.8, 137.2, 128.9, 128.5, 127.2, 126.5, 125.7, 118.6, 118.3, 54.1, 42.6, 35.9, 32.9, 31.9. Anal. Calcd for $C_{22}H_{24}N_2O_3S$: C, 66.64; H, 6.10; N, 7.07. Found: C, 66.28; H, 6.13; N, 7.03.

***N*-(2,2,4,4-Tetramethylthiochroman-6-yl)-3-[4-(trifluoromethyl)phenyl]acrylamide** (**31c**). Yield: 184mg (0.44 mmol, 88%) as a white solid, mp 185-186 ^{o}C; IR: 3272, 1662, 1532, 1323 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 10.3 (s, 1H), 8.31 (d, *J* = 8.8 Hz, 2H), 7.89 (d, *J* = 9.0 Hz, 2H), 7.80 (d, *J* = 2.1 Hz, 1H), 7.70 (d, *J* = 15.8 Hz, 1H), 7.52 (dd, *J* = 8.4, 2.2 Hz, 1H), 7.05 (d, *J* = 8.4 Hz, 1H), 7.00 (d, *J* = 15.8 Hz, 1H), 1.92 (s, 2H), 1.37 (s, 6H), 1.35 (s, 6H); ^{13}C NMR (DMSO-d_6): δ 163.5, 143.5, 139.5, 138.8, 137.2, 130.0 (q, *J* = 31.3 Hz), 129.0, 128.5, 127.2, 126.6 (q, *J* = 3.7 Hz), 125.8, 124.8 (q, *J* = 273.7 Hz), 118.6, 118.3, 54.2, 42.6, 36.0, 32.9, 31.9. Anal.Calcd for $C_{23}H_{24}F_3NOS$: C, 65.85; H, 5.77; N, 3.34. Found: C, 65.57; H, 5.79; N, 3.32.

3-(2,3,4,5,6-Pentafluorophenyl)-*N*-(2,2,4,4-tetramethylthiochroman-6-yl)acrylamide (**31d**). Yield: 207 mg (0.47 mmol, 94%) as a yellow solid, mp 143-144 °C; IR: 3276, 1664, 1523, 1498 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.80 (d, *J* = 2.0 Hz, 1H), 7.77 (d, *J* = 15.8 Hz, 1H), 7.39 (br s, 1H), 7.29 (dd, *J* = 8.4, 2.1 Hz, 1H), 7.12 (d, *J* = 8.4 Hz, 1H), 6.88 (d, *J* = 15.8 Hz, 1H), 1.95 (s, 2H), 1.42 (s, 6H), 1.40 (s, 6H); ^{13}C NMR ($CDCl_3$): δ 162.6, 145.6 (dm, *J* = 254.5 Hz), 143.7, 141.5 (dm, *J* = 264.6 Hz), 137.8 (dm, *J* = 254.5 Hz), 134.9, 129.2, 128.6, 128.5, 125.9, 118.8, 118.1, 110.7 (td, *J* = 13.1, 4.0 Hz), 54.3, 42.2, 35.8, 32.5, 31.6. Anal. Calcd for $C_{22}H_{20}F_5NOS$: C, 59.86; H, 4.57; N, 3.17. Found: C, 59.99; H, 4.75; N, 3.13.

3-(3,4-Dimethoxyphenyl)-*N*-(2,2,4,4-tetramethylthiochroman-6-yl)acrylamide (**31e**). Yield: 162 mg (0.41 mmol, 82%) as a white solid, mp 182-183 °C; IR: 3286,1660,1260 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.77 (br s, 1H), 7.68 (d, *J* = 15.4 Hz, 1H), 7.40 (br s, 1H), 7.23 (s, 1H), 7.07 (d, *J* = 8.4 Hz, 2H), 7.00 (s, 1H), 6.84 (d, *J* = 8.4 Hz, 1H), 6.43 (d, *J* = 15.4 Hz, 1H), 3.88 (s, 3H), 3.86 (s, 3H), 1.92 (s, 2H), 1.38 (s, 6H), 1.37 (s, 6H); ^{13}C NMR ($CDCl_3$): δ 164.4, 150.7, 149.1, 143.6, 141.9, 135.7, 128.5, 128.3, 127.7, 122.1, 118.9, 118.7, 118.1, 111.1, 109.9, 55.9, 55.8, 54.4, 42.2, 35.8, 32.5, 31.6. *Anal*. Calcd for $C_{24}H_{29}NO_3S$: C, 69.43; H, 7.14; N, 3.37. Found: C, 69.34; H, 7.05; N, 3.42.

3-[4-(Dimethylamino)phenyl]-*N*-(2,2,4,4-tetramethylthiochroman-6-yl)acrylamide (**31f**). Yield: 189 mg (0.48 mmol, 96%) as a yellow solid, mp 196-197 °C; IR: 3284, 1642, 1595, 1526 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.82 (br s, 1H), 7.69 (d, *J* = 15.2 Hz, 1H), 7.40 (d and obscured signal, *J* = 8.9 Hz, 3H), 7.24 (br s, 1H), 7.08 (d, *J* = 8.2 Hz, 1H), 6.65 (d and an obscured signal, *J* = 9.0 Hz, 2H), 6.35 (d, *J* = 15.6 Hz, 1H), 3.00 (s, 6H), 1.93 (s, 2H), 1.40 (s, 6H), 1.39 (s, 6H); ^{13}C NMR ($CDCl_3$): δ 164.9, 151.5, 143.5, 142.6, 135.8, 129.5, 128.4, 127.8, 122.5, 118.6, 118.0, 115.3, 111.8, 54.4, 42.1, 40.1, 35.8, 32.5, 31.5. Anal. Calcd for $C_{24}H_{30}N_2OS$: C, 73.06; H, 7.66; N, 7.10. Found: C, 72.85; H, 7.70; N, 7.08.

4-{3-Oxo-3-[(2,2,4,4-tetramethylthiochroman-6-yl)amino]prop-1-en-1-yl}benzoic acid (**31g**). To a stirred solution of **31a** (0.1 g, 0.241 mmol) in THF (12 mL), was added lithium hydroxide (11.5 mg, 0.482 mmol) in water (8 mL), and the reaction was stirred for a 4 h at room temperature. The resulting mixture was concentrated under vacuum to 1/2 of its volume and further diluted with water (10 mL). The aqueous layer was washed with ethyl acetate (3 x 20 mL), and the resulting water layer was acidified to pH 1-2 with 6 M HCl. The final solution was extracted with ethyl acetate (3 x 20 mL). The combined organic extracts were washed with saturated aqueous NaCl (50 mL), dried ($MgSO_4$), and concentrated under vacuum to afford **31g** (88 mg, 95%) as a yellow solid, mp 219-220 ^oC. IR: 3600, 2400, 1682 cm^{-1}; ^1H NMR (DMSO-d_6): δ 13.1 (s, 1H), 10.3 (s, 1H), 8.00 (d, *J* = 8.0 Hz, 2H), 7.80 (d, *J* = 2.2 Hz, 1H), 7.73 (d, *J* = 8.1 Hz, 2H), 7.62 (d, *J* = 15.7 Hz, 1H), 7.49 (dd, *J* = 8.5, 2.2 Hz, 1H), 7.03 (d, *J* = 8.4 Hz, 1H), 6.91 (d, *J* = 15.7 Hz, 1H), 1.92 (s, 2H), 1.37 (s, 6H), 1.35 (s, 6H); ^{13}C NMR (DMSO-d_6): δ 167.3, 163.5, 143.4, 139.4, 139.2, 137.0, 131.8, 130.4, 128.3, 128.2, 127.0, 125.0, 118.4, 118.1, 54.0, 42.4, 35.8, 32.7, 31.7. *Anal*. Calcd for $C_{23}H_{25}NO_3S$: C, 69.85; H, 6.37; N, 3.54. Found: C, 69.53; H, 6.39; N, 3.53.

3-(4-Aminophenyl)-N-(2,2,4,4-tetramethylthiochroman-6-yl)acrylamide (**31h**). To a stirred solution of **31b** (0.45 g, 1.2 mmol) and iron powder (0.42 g, 7.5 mmol) in ethanol:water (4:1, 20 mL) was added NH_4Cl (0.15 g, 2.8 mmol), and the resulting mixture was refluxed for 18 h. The reaction mass was cooled to room temperature and filtered through a bed of Celite®. The Celite® was washed with ethanol (3 x 20 mL), and the solution was concentrated under vacuum at 45 ^oC to give 0.6 g of a yellow solid. The yellow solid was purified by silica gel column chromatography and eluted with dichloromethane:ethyl acetate (7:3) to afford **31h** (0.42 g, 95%) as a yellow solid, mp 115-116 ^oC. IR: 3439, 3351, 3203, 1641, 1594 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.80 (br s, 1H), 7.67 (d, *J* = 15.2 Hz, 1H), 7.42 - 7.21 (complex, 4H), 7.09 (d, *J* = 8.2 Hz, 1H), 6.64 (d, *J* = 8.4 Hz, 2H), 6.35 (d, *J* = 15.2 Hz, 1H), 3.91 (br s, 2H), 1.94 (s, 2H), 1.40 (s, 6H),

1.39 (s, 6H); ^{13}C NMR ($CDCl_3$): δ 163.7, 148.4, 143.6, 142.4, 135.7, 129.7, 128.5, 128.1, 125.0, 118.7, 118.1, 116.5, 114.9, 54.4, 42.1, 35.8, 32.5, 31.6. Anal. Calcd for $C_{22}H_{26}N_2OS$: C, 72.09; H, 7.15; N, 7.64. Found: C, 71.74; H, 7.17; N, 7.61.

General procedure for synthesizing benzamides (**33a-c**). To a stirred solution of acid **31g** (198 mg, 0.5 mmol) in *N*,*N*-dimethylformamide (5 mL) was added diisopropylethylamine (1.5 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (0.55 mmol), and 1-hydroxylbenzotriazole (0.55 mmol). After stirring for 1 h at room temperature, the corresponding amine **32 a, b or c** (0.55 mmol) was added. The resulting mixture was stirred at room temperature for 12 h. The mixture was poured into ice (approx. 100 g) and stirred for 30 min. The aqueous layer was then extracted with ethyl acetate (3 x 100 mL). The combined organic extracts were washed with saturated aqueous NaCl (2 x 50 mL), dried ($MgSO_4$), and concentrated under vacuum to afford the crude benzamides. The compounds were further purified *via* a silica gel column chromatography using hexanes:ethyl acetate (1:1) to afford the desired pure benzamides **33a - c**.

***N*-Methyl-4-{3-oxo-3-[(2,2,4,4-tetramethylthiochroman-6-yl)amino]prop-1-en-1-yl}benzamide** (**33a**). Yield: 182 mg (0.445 mmol, 89%) as a yellow solid, mp 273-274 °C; IR: 1628, 1529, 1475, 1313 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 10.2 (s, 1H), 8.50 (d, *J* = 4.7 Hz, 1H), 7.89 (d, *J* = 8.2 Hz, 2H), 7.79 (d, *J* = 1.5 Hz, 1H), 7.69 (d, *J* = 8.2 Hz, 2H), 7.60 (d, *J* = 15.6 Hz, 1H), 7.49 (dd, *J* = 8.2, 1.6 Hz, 1H), 7.03 (d, *J* = 8.6 Hz, 1H), 6.88 (d, *J* = 15.6 Hz, 1H), 2.79 (d, *J* = 3.9 Hz, 3H), 1.91 (s, 2H), 1.35 (s, 6H), 1.34 (s, 6H); ^{13}C NMR (DMSO-d_6): δ 166.4, 163.5, 143.3, 139.4, 137.7, 137.1, 135.6, 128.3, 128.2, 128.0, 126.9, 124.3, 118.3, 118.1, 54.0, 42.4, 35.8, 32.7, 31.7, 26.7. *Anal*. Calcd for $C_{24}H_{28}N_2O_2S$: C, 70.56; H, 6.91; N, 6.86. Found: C, 70.28; H, 6.78; N, 6.83.

***N*-Cyclopropyl-4-{3-oxo-3-[(2,2,4,4-tetramethylthiochroman-6-yl)amino]prop-1-en-1-yl}benzamide.** (**33b**). Yield: 202 mg (0.465 mmol, 93%) as a yellow solid, mp 228-229 °C; IR:

1635, 1531 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 10.2 (s, 1H), 8.48 (d, *J* = 4.3 Hz, 1H), 7.86 (d, *J* = 8.2 Hz, 2H), 7.77 (d, *J* = 2.0 Hz, 1H), 7.66 (d, *J* = 8.2 Hz, 2H), 7.58 (d, *J* = 15.6 Hz, 1H), 7.48 (dd, *J* = 8.6, 2.2 Hz, 1H), 7.01 (d, *J* = 8.6 Hz, 1H), 6.87 (d, *J* = 15.6 Hz, 1H), 2.86 (m, 1H), 1.89 (s, 2H), 1.34 (s, 6H), 1.32 (s, 6H), 0.68 (m, 2H), 0.56 (m, 2H); ^{13}C NMR (DMSO-d_6): δ 167.0, 163.3, 143.1, 139.1, 137.5, 136.9, 135.3, 128.1, 127.7, 126.7, 124.1, 118.1, 117.8, 53.7, 42.2, 35.5, 32.5, 31.5, 23.3, 6.0 (1 aromatic C unresolved). *Anal*. Calcd for $C_{26}H_{30}N_2O_2S$: C, 71.86; H, 6.96; N, 6.45. Found: C, 71.56; H, 6.84; N, 6.31.

3-[4-(Morpholine-4-carbonyl)phenyl]-*N*-(2,2,4,4-tetramethylthiochroman-6-yl)acrylamide (**33c**). Yield: 211 mg (0.455 mmol, 91%) as a yellow solid, mp 181-182 ºC; IR: 1614, 1530, 1470, 1278, 1115 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 8.19 (br s, 1H), 7.87 (br s, 1H), 7.66 (d, *J* = 15.3 Hz, 1H), 7.44 (d, *J* = 8.2 Hz, 2H), 7.39 (d, *J* = 8.2 Hz, 2H), 7.34 (d, *J* = 7.0 Hz, 1H), 7.10 (d, *J* = 8.5 Hz, 1H), 6.48 (d, *J* = 15.3 Hz, 1H), 3.77 - 3.46 (m, 8H), 1.95 (s, 2H), 1.41 (s, 6H), 1.40 (s, 6H); ^{13}C NMR (DMSO-d_6): δ 170.0, 163.5,158.1, 143.5, 140.2, 136.5, 136.0, 135.6, 128.5, 128.1, 127.5, 122.8, 118.7, 118.0, 66.8, 54.4, 42.1, 35.8, 32.5, 31.5 (1 aliphatic C unresolved). *Anal*. Calcd for $C_{27}H_{32}N_2O_3S$: C, 69.80; H, 6.94; N, 6.03. Found: C,69.53; H, 6.96; N, 6.01. 1.2b

1.6.2 Altering the linker unit *N*-benzylthioacetamide

General methods: Commercial anhydrous *N*,*N*-dimethylformamide was stored under dry N_2 and transferred by syringe into reactions when needed. Tetrahydrofuran was dried over potassium hydroxide pellets and distilled from lithium aluminum hydride prior to use. All other commercial reagents and solvents were used as received. Unless otherwise indicated, all reactions were carried out under dry N_2 in oven-dried glassware. Reactions were monitored by thin layer chromatography (TLC, Analtech No 21521) using silica gel GF plates. Preparative separations were performed by column chromatography on silica gel (Davisil®, grade 62, 60 - 200 mesh) containing UV-active phosphor (Sorbent Technologies No UV-05) slurry packed into quartz columns. Band elution for all chromatographic separations was monitored using a hand-held UV

lamp. Melting points were uncorrected. IR spectra were run as chloroform solutions on NaCl disks. The ^{1}H- and ^{13}C-NMR spectra were measured in the indicated solvent at 400 MHz and 100 MHz, respectively, using tetramethylsilane as the internal standard with coupling constants (*J*) given in Hz.

4-Bromo-3-methylphenyl 3-methylbut-2-enoate (**36**). A clean, dried 100-mL, three-necked, round-bottomed flask fitted with a nitrogen inlet, an addition funnel and a stopper was charged 60% sodium hydride in mineral oil (1.28 g, 32.0 mmol). The oil was removed from NaH by washing with 2 x 20 mL of hexane. The sodium hydride was suspended in 25 mL of THF and cooled to 0 ^{o}C, at which time **34** (5.0 g, 26.7 mmol) in 10 mL of THF was added dropwise. The reaction was stirred for 15 min at 0 ^{o}C and **35** (3.0 g, 26.7 mol) in 15 mL THF was added dropwise. The reaction was warmed to room temperature gradually and stirred for 18 h. The crude reaction mixture was carefully poured into an ice-cold water and extracted with ether (3 x 25 mL). The combined organic layers were washed with saturated NaCl solution, and dried ($MgSO_4$) and concentrated under vacuum to afford product **36** (6.9 g, 25.6 mmol, 96%) as a colorless oil. IR: 1735, 1647, 1123 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.50 (d, *J* = 8.5 Hz, 1H), 6.99 (d, *J* = 2.0 Hz, 1H), 6.81 (dd, *J* = 8.5, 2.5 Hz, 1H), 5.89 (s, 1H), 2.38 (s, 1H), 2.22 (s, 3H), 1.00 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 164.6, 160.5, 149.7, 139.1, 132.9, 124.2, 121.1, 120.8, 114.9, 27.7, 23.1, 20.5.

6-Bromo-4,4,7-trimethylchroman-2-one (**37**). A clean, dried 250-mL three-necked, round-bottomed flask fitted with a nitrogen inlet, an addition funnel and a stopper was charged with aluminum chloride (4.75 g, 36.0 mmol) and 80 mL of dichloromethane. The resulting suspension was cooled to 0 ^{o}C and **36** (6.0 g, 22.3 mmol) in 40 mL dichloromethane was added dropwise. The ice bath was removed after the addition, and the mixture was allowed to stir at room temperature for 24 h. After TLC analysis indicated the complete absence of starting material, the reaction was quenched by dropwise addition of ice-cold 1 M HCl solution. The organic layer was

separated, and the aqueous layer was extracted with ether (2 x 75 mL). The combined organic layers were washed successively with saturated aqueous $NaHCO_3$, saturated aqueous NaCl, dried ($MgSO_4$) and concentrated under vacuum. The required regioisomer **37** was separated from **37a** by column chromatography and eluted with hexanes:ether (4:1) to afford **37** (3.5 g, 13.2 mmol, 59%) as a yellow solid, mp 87-88 ^oC; IR: 1778, 1373, 1085 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.44 (s, 1H), 6.94 (s, 1H), 2.60 (s, 2H), 2.37 (s, 3H), 1.34 (s, 6H); ^{13}C NMR (100 MHz): δ 167.6, 149.6, 138.1, 131.1, 128.1, 119.8, 119.2, 43.4, 33.2, 27.6, 22.6.

6-Bromo-4,4,5-trimethylchroman-2-one (**37a**). Yield: 1.2 g (4.5 mmol, 20%) as a yellow solid, mp 97–101 ^oC; IR: 1785, 1771, 1237 cm^{-1}; ^1H NMR (400 MHz): δ 7.46 (d, *J* = 8.0 Hz, 1H)), 6.80 (d, *J* = 8.0 Hz, 1H), 2.60 (s, 2H), 2.57 (s, 3H), 1.48 (s, 6H); ^{13}C NMR (100 MHz): δ 167.5, 150.7, 136.0, 132.0, 122.5, 116.9, 45.7, 36.0, 27.5, 22.7.

4-Bromo-2-(4-hydroxy-2,4-dimethylpentan-2-yl)-5-methylphenol (**38**). A clean, dried 250-mL three-neck, round-bottomed flask fitted with a nitrogen inlet, an addition funnel and a stopper was charged with **37** (3.5 g, 13.0 mmol) and 20 mL ether. The resulting solution was cooled to 0 ^oC, and 1.6 M methyllithium solution in ether (20.3 mL, 32.5 mmol) was added dropwise over a period of 30 min. The suspension was stirred at room temperature for 48 h and quenched with saturated aqueous NH_4Cl at 0 ^oC. The resulting suspension was diluted with ether and the organic layers were separated. The product was extracted in ether and the combined organic layers, were washed with saturated aqueous NaCl, dried ($MgSO_4$) and concentrated. The crude product was purified by column chromatography and eluted with hexane:ether (1:1) to give **38** (3.17 g, 10.53 mmol, 81%) as a white solid, mp 134-137 ^oC. IR: 3547, 3245, 2968, 1396, 1382 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.38 (s, 1H), 6.55 (s, 1H), 2.26 (s, 3H), 2.17 (s, 2H), 1.82 (br s, 1H), 1.43 (s, 6H), 1.15 (s, 6H); ^{13}C NMR ($CDCl_3$): δ 154.1, 136.7, 134.6, 131.2, 120.0, 115.5, 73.4, 52.5, 37.3, 31.1, 31.0, 22.2.

6-Bromo-2,2,4,4,7-pentamethylchromane (**39**). A clean, dried 100-mL, one-neck round-bottomed flask fitted with refluxed condenser and a nitrogen inlet was charged with **38** (3 g, 9.96 mmol) and 20 mL of phosphoric acid. The resulting mixture was heated to 110 ^{o}C for 1 h. The reaction mixture cooled to room temperature and poured into an Erlenmeyer flask containing crushed ice. The product was extracted with ether (3 x 50 mL), and the combined organic layers were washed with saturated aqueous $NaHCO_3$, saturated aqueous NaCl, dried ($MgSO_4$) and concentrated. The crude product was purified by column chromatography and eluted with hexane:ether (3:2) to give **39** (2.5 g, 8.7 mmol, 90%) as a colorless oil. IR: 1555, 1478, 1374, 1165 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.37 (s, 1H), 6.68 (s, 1H), 2.29 (s, 3H), 1.79 (s, 2H), 1.33 (s, 6H), 1.31 (s, 6H); ^{13}C NMR ($CDCl_3$): δ 151.7, 136.3, 131.2, 130.2, 120.1, 115.4, 74.7, 48.9, 32.8, 30.8, 28.5, 22.5.

2,2,4,4,7-Pentamethylchromane-6-carbonitrile (**40**). A clean, dried 250-mL Chemglass® pressure vessel (CG-1880-R-03) was charged with **39** (2.5 g, 8.7 mmol), copper cyanide (1.6 g, 17.4 mmol), L-proline (1.0 g, 8.7 mmol) and 25 mL of DMF. The reaction vessel was closed and heated to 110 ^{o}C for 24 h. The reaction mass was cooled to room temperature, filtered through Celite® and washed with ethyl acetate. The organic layer was separated, and the filtrate was extracted further using ethyl acetate, which was dried ($MgSO_4$) and concentrated under vacuum. The resulting dark brown residue was purified by column chromatography to provide **40** (1.26 g, 5.5 mmol, 63%) as a yellow oil. IR: 2217, 1615, 1495, 1149 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.49 (s, 1H), 6.69 (s, 1H), 2.42 (s, 3H), 1.84 (s, 2H), 1.36 (s, 6H), 1.34 (s, 6H); ^{13}C NMR ($CDCl_3$): δ 156.3, 140.9, 132.1, 130.0, 119.5, 119.0, 104.4, 75.8, 48.4, 32.5, 30.6, 28.5, 20.0.

(2,2,4,4,7-Pentamethylchroman-6-yl)methanamine (**41**). A clean, dried 100-mL three-necked, round bottomed flask fitted with reflux condenser and a nitrogen inlet was charged with **40** (1.2 g, 5.2 mmol) and tetrahydrofuran (20 mL). The resulting solution was cooled to 0 ^{o}C and lithium aluminum hydride (0.4 g, 10.4 mmol) was added lot-wise. The resulting slurry was allowed to

warm up to room temperature and slowly heated to reflux temperature with stirring for 4 h. At 0 ^{o}C, water (10 mL), 3 N NaOH (10 mL) and water (10 mL) were slowly added in sequence. The reaction mass was filtered through a Celite® bed and washed with ethyl acetate. The layers was separated and the aqueous phase was extracted with ethyl acetate (3 x 70 mL). The combined organic layers were dried (Na_2SO_4), concentrated under vacuum and purified by column chromatography (dichloromethane/methanol 19:1) to provide **41** (0.86 g, 3.7 mmol,71%) as a yellow oil. IR: 3437, 3365, 1567, 1156 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.18 (s, 1H), 6.61 (s, 1H), 3.81 (s, 2H), 2.28 (s, 3H), 1.81 (s, 2H), 1.33 (s, 12H); ^{13}C NMR ($CDCl_3$): δ 151.3, 134.6, 132.5, 128.9, 126.1, 119.5, 74.3, 49.3, 43.7, 32.9, 30.6, 28.5, 18.5.

General procedure for amide formation (**43a-c**). To a stirred solution of **42a-c** (1.44 mmol) in dimethylformamide (5.0 mL), was added EDC.HCl (280 mg, 1.44 mmol) and DIPEA (0.37 mL, 2.14 mmol), and the mixture was stirred at room temperature for 30 min. To the resulting solution was added HOBt (139 mg, 1.44 mmol) and **41** (200 mg, 1.2 mmol) and stirring was continued at room temperature until TLC analysis indicated the complete consumption of starting material. The reaction mass was poured into water, and the product was extracted with ethyl acetate (2 x 30 mL). The combined organic layers were washed successively with saturated aqueous $NaHCO_3$, saturated aqueous NaCl, and water. The organic layer was dried ($MgSO_4$), filtered and concentrated. The amide product was purified by column chromatography.

2-(4-Nitrophenyl)-*N*-((2,2,4,4,7-pentamethylchroman-6-yl)methyl)acetamide (**43a**). Yield: 295 mg (0.74 mmol, 62%) as a yellow solid, mp 136-137 ^{o}C; IR: 3284, 1645, 1520, 1346 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 8.20 (d, *J* = 8.4 Hz, 2H), 7.48 (d, *J* = 8.4 Hz, 2H), 7.01 (s, 1H), 6.61 (s, 1H), 5.50 (s, 1H), 4.36 (d, *J* = 5.1 Hz, 2H), 3.65 (s, 2H), 2.17 (s, 3H), 1.80 (s, 2H), 1.34 (s, 6H), 1.28 (s, 6H); ^{13}C NMR ($CDCl_3$): δ 168.5, 152.2, 147.2, 142.4, 135.5, 130.1, 129.1, 127.6, 127.2, 124.0, 119.7, 74.5, 49.0, 43.3, 42.1, 32.8, 30.5, 28.5, 18.6; *Anal.* Calcd. for $C_{23}H_{28}N_2O_4$: C, 69.68; H, 7.12; N, 7.07. Found: C, 69.32; H, 7.35; N, 7.18.

***N*-((2,2,4,4,7-Pentamethylchroman-6-yl)methyl)-2-(4-(trifluoromethyl)phenyl)acetamide** (**43b**). Yield: 302 mg (0.72 mmol, 60%) as a white solid, mp 143-144 °C; IR: 3277, 1643, 1325, 1125 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.60 (d, *J* = 7.9 Hz, 2H), 7.42 (d, *J* = 7.9 Hz, 2H), 6.96 (s, 1H), 6.60 (s, 1H), 5.47 (br s, 1H), 4.35 (d, *J* = 5.2 Hz, 2H), 3.62 (s, 2H), 2.15 (s, 3H), 1.79 (s, 2H), 1.32 (s, 6H), 1.26 (s, 6H); ^{13}C NMR ($CDCl_3$): δ 169.3, 152.0, 139.0, 135.3, 129.6, 129.5, 129.0, 127.5, 127.2, 125.8 (q, *J* = 272.1 Hz), 119.7, 74.5, 49.0, 43.5, 41.9, 32.7, 30.5, 28.5, 18.6; *Anal.* Calcd. for $C_{24}H_{28}F_3NO_2$: C, 68.72; H, 6.73; N, 3.34. Found: C, 68.95; H, 6.57; N, 3.03.

***N*-((2,2,4,4,7-Pentamethylchroman-6-yl)methyl)-2-(4-(trifluoromethoxy)phenyl)acetamide** (**43c**). Yield: 340 mg (0.78 mmol, 65%) as a white solid, mp 102-103 °C; IR: 3276, 1643, 1261, 1223 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.32 (d, *J* = 8.3 Hz, 2H), 7.18 (d, *J* = 8.3 Hz, 2H), 6.98 (s, 1H), 6.60 (s, 1H), 5.45 (s, 1H), 4.35 (d, *J* = 5.2 Hz, 2H), 3.58 (s, 2H), 2.15 (s, 3H), 1.79 (s, 2H), 1.32 (s, 6H), 1.27 (s, 6H); ^{13}C NMR ($CDCl_3$): δ 169.8, 152.0, 148.4, 135.4, 133.7, 130.7, 129.0, 127.5, 127.2, 121.4, 120.4 (q, J = 256.9 Hz), 119.7, 74.5, 49.0, 43.0, 41.9, 32.8, 30.5, 28.5, 18.5; *Anal.* Calcd. for $C_{24}H_{28}F_3NO_3$: C, 66.19; H, 6.48; N, 3.22. Found: C, 65.89; H, 6.54; N, 3.45.

2-(4-Nitrophenyl)-*N*-((2,2,4,4,7-pentamethylchroman-6-yl)methyl)ethanethioamide (**44**). To a stirred solution of **43a** (200 mg, 0.5 mmol) in tetrahydrofuran (5.0 mL) was added Lawesson's reagent (102 mg, 0.25 mmol) at room temperature, and the reaction was heated at reflux for 6 h. The crude reaction mixture was cooled to room temperature, concentrated under vacuum and purified by column chromatography (hexanes:ethyl acetate 2:1) to afford **27** (149 mg, 0.36 mmol, 72%) as a yellow solid, mp 68-70 °C. IR: 3332, 1520, 1346 cm^{-1}; ^1H NMR ($CDCl_3$): δ 8.19 (d, *J* = 8.3 Hz, 2H), 7.50 (d, *J* = 8.3 Hz, 2H), 7.07 (br s, 1H), 7.05 (s, 1H), 6.63 (s, 1H), 4.67 (d, *J* = 4.5 Hz, 2H), 4.13 (s, 2H), 2.13 (s, 3H), 1.80 (s, 2H), 1.33 (s, 6H), 1.28 (s, 6H); ^{13}C NMR ($CDCl_3$): δ 199.3, 152.7, 147.4, 143.2, 135.8, 130.0, 129.4, 128.4, 125.6, 124.0, 119.9, 74.7, 52.5, 49.2, 48.9, 32.8, 30.5, 28.5, 18.6; *Anal.* Calcd. for $C_{23}H_{28}N_2O_3S$: C, 66.96; H, 6.84; N, 6.79. Found: C, 67.13; H, 6.92; N, 6.54.

1.6.3 Altering the linker with thiazoline ring

General methods: Commercial anhydrous *N*,*N*-dimethylformamide was stored under dry N_2 and transferred by syringe into reactions when needed. Tetrahydrofuran was dried over potassium hydroxide pellets and distilled from lithium aluminum hydride prior to use. All other commercial reagents and solvents were used as received. Unless otherwise indicated, all reactions were carried out under dry N_2 in oven-dried glassware. Reactions were monitored by thin layer chromatography (TLC, Analtech No 21521) using silica gel GF plates. Preparative separations were performed by column chromatography on silica gel (Davisil®, grade 62, 60 - 200 mesh) containing UV-active phosphor (Sorbent Technologies No UV-05) slurry packed into quartz columns. Band elution for all chromatographic separations was monitored using a hand-held UV lamp. Melting points were uncorrected. IR spectra were run as chloroform solutions on NaCl disks. The ^{1}H- and ^{13}C-NMR spectra were measured in the indicated solvent at 400 MHz and 100 MHz, respectively, using tetramethylsilane as the internal standard with coupling constants (*J*) given in Hz.

4-((4-Bromophenyl)thio)-4-methylpentan-2-one (**47**). To a stirred solution of 4-bromothiophenol (**46**) (5.0 g, 26.4 mmol) in chloroform (35 mL) was added trimethylamine (3.5 mL, 26.4 mmol), followed by mesityl oxide (**25**) (3.0 mL, 26.4 mmol). The resulting solution was heated to reflux (bath temperature 70 ºC). Two additional portions of trimethylamine (3.5 mL, 26.4 mmol) and mesityl oxide (3.0 mL, 26.4 mmol) were added at regular intervals of 4 h, and the resulting solution was cooled, filtered through Celite® and washed with dichloromethane (2 x 25 mL). The combined organic layers were washed with water (2 x 50 mL), saturated aqueous NaCl, dried ($MgSO_4$), and concentrated to give the crude product as a yellow oil. The crude material was purified by column chromatography (hexanes/ether 2:1) to afford **47** (6.8 g, 23.8 mmol, 90%) as a colorless oil; IR: 1713, 1468, 1010 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.48 (d, *J* =

8.4 Hz, 2H), 7.39 (d, *J* = 8.3 Hz, 2H), 2.65 (s, 2H), 2.15 (s, 3H), 1.38 (s, 6H); ^{13}C NMR ($CDCl_3$): δ 206.4, 139.1, 131.9, 130.6, 124.0, 54.3, 47.4, 32.2, 28.2.

4-((4-Bromophenyl)thio)-2,4-dimethylpentan-2-ol (**48**). To a stirred solution of methyllithium in ether (478.0 mL, 34.8 mmol, 1.6 M) at -50 ^{o}C was added dropwise **47** (5 g, 17.4 mmol) in tetrahydrofuran (75 mL) over 30-45 min. The resulting reaction mixture was warmed to room temperature and stirred for 3 h. The reaction mixture was then cooled to 0 ^{o}C, and quenched by dropwise addition of saturated NH_4Cl solution (20 mL), and the solution was extracted with ethyl acetate (3 x 50 mL). The combined organic extracts were washed with saturated aqueous NaCl (50 mL), dried ($MgSO_4$), and concentrated under vacuum to afford a dark brown liquid. The crude product was purified by column chromatography (hexane/ether 1:1) to afford **48** (4.2 g, 13.9 mmol, 80%) as a colorless oil; IR: 3450, 1468, 1010 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.46 (s, 4H), 3.19 (br s, 1H), 1.79 (s, 2H), 1.37 (s, 6H), 1.33 (s, 6H); ^{13}C NMR ($CDCl_3$): δ 138.8, 131.8, 130.8, 123.8, 71.9, 52.4, 49.5, 32.2, 30.9.

6-Nitro-*N*-(2,2,4,4-tetramethylthiochroman-6-yl)benzo[*d*]thiazol-2-amine (**45**). To a stirred solution of **48** (4.0 g, 13.2 mmol) in dichloromethane (40 mL) at room temperature was added portion-wise anhydrous aluminum chloride (2.1 g, 15.8 mmol) over a period of 30 min, and reaction was refluxed for 1 h. The reaction mixture was cooled to 0 ^{o}C and quenched with ice cold water (20 mL) to give a suspension which was, filtered through Celite® and washed with dichloromethane (30 mL). The layers were separated, and the aqueous layer was extracted with dichloromethane (2 x 20 mL). The combined organic extracts were washed with saturated aqueous NaCl, dried ($MgSO_4$) and concentrated to give **49** as brown residue.

The residue was dissolved in dimethylformamide (30 mL) and transferred to a 250 mL Chemglass® pressure vessel (CG-1880-R-03). To the resulting solution was added potassium carbonate (3.6 g, 26.4 mmol), copper iodide (0.5 g, 2.64 mmol), L-proline (0.6 g, 5.28 mmol) and 6-nitrobenzo[*d*]thiazole-2-amine (**50**) (3.1 g, 15.84 mmol). The reaction vessel was immersed

into a pre-heated oil bath at 140 °C and stirred for 18 h. The crude reaction mixture cooled to room temperature and poured into water (100 mL), filtered through Celite®, and washed with ethyl acetate (50 mL). The layers were separated and the aqueous phase was extracted with ethyl acetate (2 x 25 mL), dried ($MgSO_4$) and concentrated under vacuum to provide brown oil. The product was purified by column chromatography (hexanes:ether 1:1) to afford **45** as a orange solid (3.7 g, 9.2 mmol, 70%), mp 59-60 °C. IR: 3210, 2247, 1341 cm^{-1}; ^1H NMR ($CDCl_3$): δ 8.41 (d, *J* = 2.5 Hz, 1H), 8.31 (dd, *J* = 8.3, 4.4 Hz, 2H), 7.43 (d, *J* = 8.9 Hz, 1H), 7.29 (d, *J* = 2.5 Hz, 1H), 7.21 (br s, 1H), 7.07 (d, *J* = 8.2 Hz,1H), 6.80 (dd, *J* = 8.2, 2.1 Hz, 2H), 1.94 (s, 2H), 1.42 (s, 6H), 1.37 (s, 6H); ^{13}C NMR ($CDCl_3$): δ 144.7, 144.1, 143.5, 134.4, 129.5, 128.2, 127.4, 126.9, 126.3, 121.3, 115.2, 53.8, 42.4, 35.8, 32,4, 31.6. *Anal.* Calcd. for $C_{20}H_{21}N_3O_2S_2$: C, 60.13; H, 5.30; N, 10.52. Found: C, 60.28; H, 5.12; N, 10.76.

1.6.4 Synthesizing nitrogen containing heteroarotinoids

General methods: Commercial anhydrous *N*,*N*-dimethylformamide was stored under dry N_2 and was transferred by syringe into reactions when needed. Tetrahydrofuran was dried over potassium hydroxide pellets and distilled from lithium aluminum hydride prior to use. All other commercial reagents and solvents were used as received. Unless otherwise indicated, all reactions were carried out under dry N_2 in oven-dried glassware. Reactions were monitored by thin layer chromatography (TLC, Analtech No 21521) using silica gel GF plates. Preparative separations were performed by column chromatography on silica gel (Davisil®, grade 62, 60 - 200 mesh) containing UV-active phosphor (Sorbent Technologies, No UV-05) slurry packed into quartz columns. Band elution for all chromatographic separations was monitored using a hand-held UV lamp. Melting points were uncorrected. IR spectra were run as chloroform solutions on NaCl disks or in nujol. The ^1H- and ^{13}C-NMR spectra were measured in the indicated solvent at 400 MHz and 100 MHz, respectively, using tetramethylsilane as the internal standard with coupling constants (*J*) given in Hz.

***N*-(4-Bromophenyl)-3-methylbut-2-enamide** (**65**). A solution of 3-methylbut-2-enoyl chloride (3.4 mL, 29.0 mmol) in chloroform (25 mL) was added dropwise to a stirred solution of 4-bromoaniline (**64**) (10 g, 58.1 mmol) in chloroform (250 mL). The resulting cloudy reaction mixture was refluxed for 5 h, and then cooled to room temperature and filtered through Celite®. The filtrate was washed with 1 M HCl (100 mL), saturated aqueous $NaHCO_3$, and saturated aqueous NaCl, dried ($MgSO_4$), concentrated under vacuum and recrystallized from ethanol to afford **65** as a white solid (5.5 g, 21.8 mmol, 75%), mp 118-119 ^oC; IR: 3294, 1663, 1643, 826 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.43 (s, 4H), 7.01 (br s, 1H), 5.69 (s, 1H), 2.22 (s, 3H), 1.91 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 154.4, 151.4, 137.3, 131.9, 118.3, 27.4, 20.0.

***N*-(4-Bromophenyl)-3-methylbut-3-enamide** (**65a**). A solution of 3-methylbut-2-enoyl chloride (3.4 mL, 12.7 mmol) in chloroform (5 mL) was added dropwise to a stirred, ice-cooled solution containing 4-bromoaniline (**64**) (2.0 g, 11.6 mmol) and triethylamine (3.23 mL, 23.2 mmol) in dichloromethane (25 mL). The reaction was stirred at room temperature for 18 h and then diluted with dichloromethane (25 mL), washed with water (3 x 50 mL), saturated aqueous NaCl (50 mL). The organic phase was dried ($MgSO_4$) and concentrated under vacuum to provide **65a** as a yellow solid (2.5 g, 10.1 mmol, 87%), mp 108-110 ^oC; IR: 3288, 1660, 1392, 814 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.42 (s, 4H), 5.09 (s, 1H), 5.01 (s, 1H), 3.12 (s, 2H), 1.85 (s, 3H); ^{13}C NMR (100 MHz): δ 168.4, 140.2, 136.8, 132.0, 121.3, 116.9, 116.5, 47.5, 22.5.

6-Bromo-4,4-dimethyl-3,4-dihydroquinolin-2(1*H*)-one (**66**). To a stirred solution of **65** (5.0 g, 19.6 mmol) in dichloroethane was added aluminum chloride (3.9 g, 29.5 mmol) portion-wise and the mixture was heated to reflux for 1 h. The reaction was cooled to 0 ^oC, quenched with ice-cold water (20 mL), filtered through Celite® and washed with dichloromethane (2 x 50 mL). The layers were separated, washed the organic phase with saturated aqueous $NaHCO_3$ (1 x 50 mL), saturated aqueous NaCl (1 x 50 mL) and dried ($MgSO_4$). The organic layer was concentrated under vacuum and purified by column chromatography (to afford **66** as a brown solid (3.8 g, 14.9

mmol, 76%), mp 151-153 °C; IR: 3201, 1681, 1488, 1368 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 9.36 (s, 1H), 7.39 (s, 1H), 7.27 (d, *J* = 8.4 Hz, 1H), 6.75 (d, *J* = 8.4 Hz, 1H), 2.48 (s, 2H), 1.34 (s, 6H); ^{13}C NMR ($CDCl_3$): δ 171.2, 135.1, 134.6, 130.4, 127.7, 117.5, 116.1, 44.9, 34.1, 27.5.

6-Bromo-4,4-dimethyl-1,2,3,4-tetrahydroquinoline (**67**). To a stirred, ice-cooled solution of **66** (3.5 g, 13.8 mmol) in distilled toluene (35 mL) was added borane-dimethyl sulfide complex (1.4 mL, 14.4 mmol) dropwise, and then mixture was refluxed for 3h. The reaction was cooled to room temperature and quenched carefully by dropwise addition of 10% aqueous Na_2CO_3 (10 mL). The resulting biphasic mixture was stirred at room temperature for 15 min and the layers were separated and dried ($MgSO_4$) and concentrated under vacuum and gave **67** as a colorless oil (3.0 g, 12.4 mmol, 90%), IR: 3414, 1495, 1282 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.29 (d, *J* = 2.3 Hz, 1H), 7.07 (dd, *J* = 8.3, 2.31 Hz, 2H), 6.52 (d, *J* = 8.5 Hz, 1H), 3.33 (t, *J* = 5.8 Hz, 2H), 1.76 (t, 5.8 Hz, 2H), 1.29 (s, 6H); ^{13}C NMR ($CDCl_3$): δ 140.4, 133.7, 129.5, 129.4, 117.1, 110.6, 38.4, 36.4, 32.0, 30.8.

***tert*-Butyl 6-bromo-4,4-dimethyl-3,4-dihydroquinoline-1(2*H*)-carboxylate** (**68**). A Tetrahydrofuran (50 mL) solution containing **67** (3.0 g, 12.4 mmol), was cooled to -78 °C, and 2.5 M *n*-butyllithium (6 mL, 14.9 mmol) was added dropwise over a period of 30 min. The solution was stirred for 30 min and di-*tert*-butyl dicarbonate (3.3 g, 14.9 mmol) in tetrahydrofuran (15 mL) was added dropwise over a period of 30 min. The reaction was allowed to attain room temperature gradually, with stirring for 18 h, and then cooled to 0 °C. The reaction mixture was quenched by dropwise addition of saturated aqueous NH_4Cl solution (20 mL). The layers were separated and the aqueous phase was extracted with ether (2 x 50 mL). The combined organic extracts were dried ($MgSO_4$), concentrated and purified by column chromatography to provide **68** as a brown oil (3.8 g, 11.4 mmol, 92%), IR: 1679, 1483, 1367, 1152 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.52 (s,1H), 7.36 (d, *J* = 2.4 Hz, 2H), 7.21 (dd, *J* = 6.6, 2.3 Hz, 1H), 3.72 – 3.69 (m, 2H), 1.74 –

1.71 (m, 2H), 1.51 (s, 9H), 1.28 (s, 6H); ^{13}C NMR ($CDCl_3$): δ 153.6, 140.2, 136.3, 128.7, 128.6, 126.0, 116.4, 81.1, 41.7, 38.1, 33.4, 30.8, 30.0, 28.4.

***tert*-Butyl 6-amino-4,4-dimethyl-3,4-dihydroquinoline-1(2*H*)-carboxylate (70)**. A mixture of **68** (3.5 g, 10.3 mmol), sodium azide (1.3 g, 20.6 mmol), CuI (0.2 g, 1.03 mmol), L-proline (0.35 g, 3.1 mmol), NaOH (0.12 g, 3.14 mmol) and ethanol/water (7:3, 20mL) was heated to 90 °C in a Chemglass pressure vessel (Chem-Glass No. CG-1880-01) for 18 h. The reaction was cooled to room temperature, filtered through Celite® and washed with ethyl acetate (50 mL). The filtrate was washed with water (2 x 30 mL), saturated aqueous NaCl (1 x 50 mL), dried ($MgSO_4$) and concentrated under vacuum to provide **69** as a brown oil. The resulting brown oil was dissolved in methanol (100 mL), and 10% Pd/C (0.3 g, 10% w/w) was added under nitrogen atmosphere. The reaction vessel was flushed with hydrogen gas, and stirring was continued at room temperature under hydrogen atmosphere for 6 h. The catalyst was removed by filtering through Celite® and washing with methanol (25 mL). The filtrate was concentrated and purified by column chromatography (hexanes:ether 4:1) to afford **70** (1.8 g, 6.4 mmol, 62%) as a brown oil. IR: 3448, 3362, 1685, 1503, 1380, 1154 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.61 (d, *J* = 8.2 Hz, 1H), 7.28 (dd, *J* = 7.8, 1.6 Hz, 2H), 7.12 (td, *J* = 7.2, 1.6 Hz, 1H), 7.03 (td, *J* = 7.2, 1.6 Hz, 1H), 3.75-3.72 (m, 2H), 1.76-1.73 (m, 2H), 1.52 (s, 9H), 1.30 (s, 6H); ^{13}C NMR ($CDCl_3$): δ 154.0, 142.1, 139.1, 128.7, 125.5, 113.1, 112.2, 80.3, 41.6, 38.8, 33.2, 30.2, 28.5, 28.4.

General procedure to synthesize 73a-d. To a stirred solution of **70** (0.2 g, 0.7 mmol) in tetrahydrofuran (5 mL) was added iso(thio)cyanates **71a-d** (0.7 mmol) in tetrahydrofuran (2 mL) dropwise at room temperature under nitrogen atmosphere. The mixture was stirred until the TLC analysis indicated that **70** was completely consumed. The solvent was evaporated under vacuum to afford the Boc protected (thio)urea derivatives **72a-d**. To the resulting Boc-protected compound in dichloromethane (5 mL) was slowly added trifluoroacetic acid (200 µL, 2.6 mmol) and the mixture was stirred until TLC indicated the absence of **72a-d**. The solvent was evaporated

completely under vacuum; two additional portions of dichloromethane (2 x 10 mL) were added and then were removed under vacuum. Water (20 mL) was added to the resulting residue and the mixture was washed with ether (2 x 20 mL). The aqueous layer was basified using $NaHCO_3$ powder and extracted with ethyl acetate (3 x 20 mL). The combined organic extracts were washed with water (2 x 20 mL), saturated aqueous NaCl (1 x 20 mL), dried ($MgSO_4$) and evaporated under vacuum. The crude products were purified by recrystallization from pentane/ether to afford **73a-d.**

1-(4,4-Dimethyl-1,2,3,4-tetrahydroquinolin-6-yl)-3-(4-nitrophenyl)thiourea (**73a**). Yield: 164 mg (0.46mmol, 66%) as a red solid, mp 150-152 ºC; IR: 3333, 1509, 1334, 1263 cm^{-1}; ^1H NMR ($CDCl_3$): δ (ppm) 8.19 (d, *J* = 8.6 Hz, 2H), 7.78 (d, *J* = 8.6 Hz, 2H), 7.71 (br s, 2H), 7.09 (s, 1H), 6.88 (d, *J* = 8.3 Hz, 1H), 6.50 (d, *J* = 8.3 Hz, 2H), 4.19 (br s, 2H), 3.39-3.36 (m, 2H), 1.76-1.74 (m, 2H), 1.30 (s, 6H); ^{13}C NMR ($CDCl_3$): δ 179.5, 144.3, 144.2, 131.6, 125.1, 124.8, 124.4, 123.4, 122.7, 114.9, 38.2, 36.2, 32.0, 30.6; *Anal*. Calcd. for $C_{18}H_{20}N_4O_2S$: C, 60.65; H, 5.65; N, 15.72. Found: C, 60.53; H, 5.82; N, 15.87.

1-(4,4-Dimethyl-1,2,3,4-tetrahydroquinolin-6-yl)-3-(4-(trifluoromethyl)phenyl)thiourea (**73b**). Yield: 169 mg (0.44 mmol, 63%) as a yellow solid, mp 104-105 ºC; IR: 3346, 1512, 1324 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.65 (d, *J* = 8.2 Hz, 2H), 7.58 (d, *J* = 8.2 Hz, 2H), 7.11 (d, *J* = 4.0 Hz, 1H), 6.89 (dd, *J* = 8.0, 4.0 Hz, 1H), 6.49 (d, *J* = 8.0 Hz, 1H), 3.36 (t, *J* = 8.0 Hz, 2H), 1.75 (t, J = 8.0 Hz, 2H), 1.29 (s, 6H); ^{13}C NMR ($CDCl_3$): δ 180.1, 143.9, 141.4, 131.5, 125.9, 125.2, 124.9, 123.8, 123.4 (q, *J* = 271.5 Hz), 114.8, 38.9, 36.3, 32.0, 30.6; *Anal*. Calcd. for $C_{19}H_{20}F_3N_3S$: C, 60.14; H, 5.31; N, 11.07. Found: C, 60.28; H, 5.12; N, 11.28.

1-(4,4-Dimethyl-1,2,3,4-tetrahydroquinolin-6-yl)-3-(4-(trifluoromethoxy)phenyl)thiourea (**73c**). Yield: 164 mg (0.42 mmol, 60%) as a yellow solid, mp 69-71 ºC; IR: 3348, 3186, 1509, 1257 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.69 (br s, 1H), 7.49 (d, *J* = 12.0 Hz, 2H), 7.18 (d, *J* = 12.0 Hz, 2H), 7.11 (d, *J* = 4.0 Hz, 1H), 6.89 (dd, *J* = 8.0, 4.0 Hz, 1H), 6.48 (d, *J* = 8.0 Hz, 1H), 3.35 (t, *J* =

4.0 Hz, 2H), 1.74 (t, *J* = 4.0 Hz, 2H), 1.29 (s, 6H); ^{13}C NMR ($CDCl_3$): δ 180.4, 146.7, 143.8, 136.8, 131.4, 126.1, 125.2, 124.9, 121.3, 120.4 (q, *J* = 257.4 Hz), 114.8, 38.2, 36.3, 31.9, 307; *Anal.* Calcd. for $C_{19}H_{20}F_3N_3OS$: C, 57.71; H, 5.10; N, 10.63. Found: C, 57.56; H, 5.23; N, 10.37.

1-(4,4-Dimethyl-1,2,3,4-tetrahydroquinolin-6-yl)-3-(4-nitrophenyl)urea (**73d**). Yield: 153 mg (0.45 mmol, 64%) as a yellow solid, mp 219-220 °C; IR: 1698, 1548, 1180, 851 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 9.23 (s, 1H), 8.36 (s, 1H), 8.16 (d, *J* = 8.9 Hz, 2H), 7.66 (d, *J* = 8.9 Hz, 2H), 7.18 (s, 1H), 6.91 (d, *J* = 8.5 Hz, 1H), 6.39 (d, *J* = 8.5 Hz, 1H), 5.54 (s, 1H), 3.16 (s, 2H), 1.61 (s, 2H), 1.22 (s, 6H); ^{13}C NMR (DMSO-d_6): δ 152.6, 147.4, 141.0, 129.4, 127.6, 125.6, 119.5, 118.7, 117.6, 114.1, 37.8, 37.3, 31.9, 31.3; *Anal.* Calcd. for $C_{18}H_{20}N_4O_3$: C, 63.52; H, 5.92; N, 16.46. Found: C, 63.36; H, 6.08; N, 16.51.

1,1,4,4-Tetramethyl-6-(3-(4-nitrophenyl)ureido)-1,2,3,4-tetrahydroquinolin-1-ium iodide (**73e**). To a stirred solution of **73d** (0.2 g, 0.6 mmol) in dimethylformamide (5 mL) in a 15 mL Chemglass pressure vessel (No. CG-1880-01) was added Cs_2CO_3 (390 mg, 1.2 mmol), methyl iodide (1.0 mL, 16.0 mmol). The vessel was closed, and the reaction was stirred at room temperature for 24 h. Water (5.0 mL) was added and filtered, The solid was stirred with ethanol (10 mL) for 15 min and filtered to provide **73e** as a yellow solid (185 mg, 0.37 mmol, 62%), mp 249-251 °C; IR: 3297, 3260, 1724, 1598, 843 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 9.59 (s, 1H), 9.21 (s, 1H), 8.21 (d, *J* = 8.0 Hz, 2H), 7.88 (d, *J* = 8.0 Hz, 1H), 7.71 (d, *J* = 8.0 Hz, 2H), 7.67 (s, 1H), 7.51 (d, *J* = 12.0 Hz, 1H), 3.89 (s, 6H), 3.56 (s, 6H), 2.11(s, 2H), 1.36 (s, 6H); ^{13}C NMR ($CDCl_3$): δ 151.4, 145.4, 140.7, 139.7, 139.4, 135.0, 124.5, 121.3, 117.4, 116.7, 59.4, 56.1, 31.6, 30.5, 26.8; *Anal.* Calcd. for $C_{20}H_{25}IN_4O_3$: C, 48.40; H, 5.08; N, 11.29. Found: C, 48.65; H, 5.23; N, 11.52.

6-Bromo-2,2,4-trimethyl-1,2-dihydroquinoline (**74**). Bismuth(III) triflate (19.0 g, 30.0 mmol) was added to a solution of 4-bromoaniline (**64**) (25.0 g, 145 mmol) in acetone (500 mL), and the mixture was stirred at reflux temperature for 3 days. The solvent was removed completely under vacuum and the residue was partitioned between ether (300 mL) and water (200 mL). The layers

were separated and the aqueous phase was extracted with ether (200 mL). The organic layer was washed with saturated aqueous NaCl (200 mL) and evaporated under vacuum. The crude product was purified by column chromatography increasing concentrations of (ether in hexanes) to afford **74** as a brown solid (23 g, 89.9 mmol, 62%), mp 83-85 ^{o}C; IR: 3382, 1486, 1257, 806 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.13 (d, *J* = 2.2 Hz, 1H), 7.05 (dd, *J* = 8.4, 2.2 Hz, 1H), 6.31 (d, *J* = 8.4 Hz, 1H), 5.33 (s, 1H), 3.71 (br s, 1H), 1.95 (s, 3H), 1.26 (s, 6H); ^{13}C NMR ($CDCl_3$): δ 142.2, 130.7, 129.4, 127.6, 126.2, 123.4, 114.3, 108.6, 51.9, 30.9, 18.4.

6-Bromo-1,2,2,4-tetramethyl-1,2-dihydroquinoline (**75**). Sodium hydride (4.5 g, 113.0 mmol) was added to dimethylformamide (190 mL) under a nitrogen atmosphere, and the mixture was cooled to 15 ^{o}C. A solution of **74** (19.0 g, 75.3 mmol) in dimethylformamide (75 mL) was added dropwise, stirred for 30 min, and then methyl iodide (43 mL, 300 mmol) in dimethylformamide (75 mL) was added dropwise. The reaction was warmed to room temperature gradually and stir for 18 h. The crude reaction was added to water and extracted with ether (2 x 100 mL). The combined organic extracts were washed with saturated aqueous NaCl, dried ($MgSO_4$) and concentrated to provide the **75** (16.4 g, 62 mmol, 82%) as a yellow oil. IR: 1488, 1406, 797 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.12 (d, *J* = 8.4 Hz, 1H), 7.11 (d, *J* = 2.4 Hz, 1H), 6.36 (d, *J* = 8.4 Hz, 1H), 5.32 (d, *J* = 1.5 Hz, 1H), 2.76 (s, 3H), 1.95 (s, 3H), 1.29 (s, 6H); ^{13}C NMR ($CDCl_3$): δ 144.2, 131.2, 130.9, 127.3, 125.8, 125.2, 125.2, 112.2, 108.4, 56.3, 30.7, 27.1, 18.5.

7-Bromo-1,2,2,4-tetramethyl-1,2,3,4-tetrahydroquinolin-3-ol (**76**). A 1.0 M borane/THF solution (97.0 mmol, 98 mL) was added dropwise to an ice-cooled solution of **75** (13.0 g, 48.8 mmol) in THF (250 mL), and the mixture was stirred at 15 ^{o}C for 6 h. A 1:1 solution of THF/H_2O (60 mL) was added dropwise to the reaction mixture over 30 min, followed by dropwise addition of aqueous sodium hydroxide (3 N, 50 mL) for 30.0 min. To this mixture was added 30% aqueous hydrogen peroxide (16.0 mL) and stirring was continued at room temperature for 2 h. The crude reaction mixture was poured into water and extracted with ethyl acetate (3 x 150 mL).

The combined organic layers were washed with saturated aqueous $NaHCO_3$, saturated aqueous NaCl and dried (anhydrous Na_2SO_4). The solvent was evaporated under reduced pressure, and the residue was purified by flash chromatography (hexane/ethyl acetate 7:3) to afford **76** as a colorless oil (7.9 g, 27.8 mmol, 57%), IR: 3406, 1589, 1490 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.24 (d, *J* = 2.4 Hz, 1H), 7.17 (dd, *J* = 8.8, 2.4 Hz, 1H), 6.47 (d, *J* = 8.8 Hz, 1H), 3.27 (d, *J* = 9.36 Hz, 1H), 2.79 (s, 6H), 2.76-2.68 (m, 1H); 1.90 (br s, 1H), 1.41 (d, *J* = 10.5 Hz, 3H), 1.36 (s, 6H), 1.01 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 144.3, 129.9, 129.7, 128.2, 113.8, 109.0, 58.0, 36.1, 31.6, 24.9, 18.1, 17.0.

6-Bromo-1,2,2,4,4-pentamethyl-1,4-dihydroquinolin-3(2*H*)-one (**78**). DMSO (2.3 mL, 31.7 mmol) was added dropwise to a solution of oxalyl chloride (1.4 mL, 17.3 mmol) in dichloromethane (60 mL) at -60 ºC, and the resultant solution was stirred for 10 min. This solution was transferred *via* syringe to a solution of **76** (4.1 g, 14.4 mmol) in dichlormethane (60 mL) at -60 ºC. The mixture was stirred for 15 min, before triethylamine (10 mL, 72.0 mmol) was added dropwise over 15 min. The reaction was stirred 1 h and quenched by dropwise addition of water (20 mL). The mixture was stirred with warming to room temperature, and the layers were separated. The organic layer was washed with water (2 x 20 mL), dried ($MgSO_4$) and concentrated to give **77**. The crude obtained was used directly for next step without further purification.

To a solution of **77** in THF (20 mL) was added dropwise 26% lithium bis(trimethylsilyl)amide in THF (25 mL, 38.0 mmol) over 10 min at -50 ºC. The reaction was warmed to -20 ºC and iodomethane (2.4 mL, 38.0 mmol) in THF (20 mL) was added dropwise, and stirring was continued with warming to room temperature for 3 h. The reaction mixture was poured into ice-cold water and extracted with ethyl acetate (2 x 50 mL). The combined organic layers were washed with saturated aqueous NaCl and dried (anhydrous Na_2SO_4). Concentration under vacuum, purification by column chromatography (hexanes/ethyl acetate 3:2) gave **78** (2.6 g, 8.9

mmol, 62%) as a colorless oil. IR: 1719, 1486 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.33 (dd, *J* = 8.6, 2.3 Hz, 1H), 7.29 (d, *J* = 2.3 Hz, 1H), 6.08 (d, *J* = 8.6 Hz, 1H), 2.83 (s, 3H), 1.45 (s, 6H), 1.28 (s, 6H); ^{13}C NMR ($CDCl_3$): δ 214.4, 144.6, 132.7, 130.4, 127.5, 115.7, 112.4, 64.2, 47.6, 30.9, 23.3, 22.9.

6-Amino-1,2,2,4,4-pentamethyl-1,4-dihydroquinolin-3(2*H*)-one (**79**). Into a 250 mL Chem-glass pressure vessel (No. CG-1880-R-03) was added **78** (1.9 g, 6.42 mmol), copper iodide (0.61 g, 3.2 mmol), L-proline (0.74 g, 6.42 mmol), dimethylformamide (4.0 mL) and aqueous ammonia (19.0 mL). The reaction mixture was heated to 110 °C for 24 h and then cooled to room temperature and quenched with water (200 mL). The resulting mixture was extracted with ethyl acetate (3 x 100 mL) and the extract was dried ($MgSO_4$), concentrated under vacuum and purified by column chromatography to give **78** (0.9 g, 3.9 mmol, 65%) as a brown oil. IR: 3422, 3357, 1711, 1501 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.66-7.60 (m, 3H), 3.35 (br s, 2H), 2.78 (s, 3H), 1.44 (s, 6H), 1.25 (s, 6H); ^{13}C NMR ($CDCl_3$): δ 215.8, 139.6, 138.6, 132.0, 115.0, 114.5, 112.7, 64.3, 47.7, 31.0, 23.0.

General procedure to synthesize 80(a-f). To a stirred solution of **79** (0.2 g, 0.86 mmol) in tetrahydrofuran (5 mL), was added iso(thio)cyanates **71a-f** (0.86 mmol) in tetrahydrofuran (2 mL) dropwise at room temperature under a nitrogen atmosphere. The reaction was stirred until TLC analysis indicate the complete consumption of **57**. The solvent was evaporated under vacuum, purified by column chromatography, and crystallized from ether in pentane (3:7) to afford the **80a-f**.

1-(4-Nitrophenyl)-3-(1,2,2,4,4-pentamethyl-3-oxo-1,2,3,4-tetrahydroquinolin-6-yl)thiourea (**80a**). Yield: 0.23 g (0.56 mmol, 65%) as a yellow solid, mp 145-147 °C; IR: 3308, 1715, 1532, 1498, 1332 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 8.20 (d, *J* = 8.7 Hz, 2H), 7.83 (s, 1H), 7.75 (d, *J* = 8.7 Hz, 2H), 7.69 (s, 1H), 7.21 (dd, *J* = 8.6, 2.4 Hz, 1H), 7.14 (d, *J* = 2.4 Hz, 1H), 6.88 (d, *J* = 8.5 Hz, 1H), 2.91 (s, 3H), 1.45 (s, 6H), 1.32 (s, 6H); ^{13}C NMR ($CDCl_3$): δ 213.6, 179.4, 145.7, 144.5,

144.0, 132.7, 127.0, 125.7, 124.5, 123.0, 122.8, 115.1, 64.4, 47.7, 31.1, 23.7, 23.0; *Anal.* Calcd. for $C_{21}H_{24}N_4O_3S$: C, 61.15; H, 5.86; N, 13.58. Found: C, 61.38; H, 5.52; N, 13.37.

1-(1,2,2,4,4-Pentamethyl-3-oxo-1,2,3,4-tetrahydroquinolin-6-yl)-3-(4-trifluoromethyl)phenyl)thiourea (**80b**). Yield: 0.25 g (0.58 mmol, 67%) as a brown solid, mp 149-151 ^oC; IR: 3291, 3206, 1716, 1615, 1324 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.88 (s, 1H), 7.65 (s, 1H), 7.60 (s, 4H), 7.22 (dd, *J* = 8.5, 2.6 Hz, 1H), 7.15 (d, *J* = 2.4 Hz, 2H), 7.15 (d, *J* = 8.5 Hz, 1H), 2.90 (s, 6H), 1.48 (s, 6H), 1.32 (s, 6H); ^{13}C NMR ($CDCl_3$): δ 214.0, 179.8, 145.3, 141.1, 132.3, 126.05 (q, *J* = 1.2 Hz), 125.6, 124.1, 123.9 (q, *J* = 272.0 Hz), 122.7, 115.0, 64.4, 47.6, 31.1, 23.6, 23.0. *Anal.* Calcd. for $C_{22}H_{24}F_3N_3OS$: C, 60.67; H, 5.55; N, 13.09. Found: C, 60.94; H, 5.23; N, 13.28.

1-(1,2,2,4,4-Pentamethyl-3-oxo-1,2,3,4-tetrahydroquinolin-6-yl)-3-(4-(trifluoromethoxy)phenyl)thiourea (**80c**). Yield: 0.24 g (0.52 mmol, 60%) as a brown solid; mp 83-85 ^oC; IR: 3291, 3213, 1716, 1501 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.70 (s, 1H), 7.52 (s, 1H), 7.47 (d, *J* = 8.7, 2.0 Hz, 2H), 7.24-7.20 (m, 3H), 7.15 (d, *J* = 2.4 Hz, 1H), 6.85 (d, *J* = 8.5 Hz, 1H), 2.89 (s, 3H), 1.48 (s, 6H), 1.31 (s, 6H); ^{13}C NMR ($CDCl_3$): δ 214.0, 147.1, 145.3, 136.4, 132.2, 128.0 (q, *J* = 2.4 Hz), 126.5, 125.9, 122.9, 121.6, 121.1 (q, *J* = 257.3 Hz), 114.9, 64.4, 47.6, 31.0, 23.6, 23.0. *Anal.* Calcd. for $C_{22}H_{24}F_3N_3O_2S$: C, 58.52; H, 5.36; N, 9.31. Found: C, 58.29; H, 5.12; N, 9.07.

1-(4-Nitrophenyl)-3-(1,2,2,4,4-pentamethyl-3-oxo-1,2,3,4-tetrahydroquinolin-6-yl) urea (**80d**). Yield: 0.25 g (0.64 mmol, 74%) as an orange solid, mp 200-201 ^oC; IR (nujol): 1718, 1655, 1556 cm^{-1}; ^1H NMR (DMSO-d_6): δ 9.35 (s, 1H), 8.73 (s, 1H), 8.18 (d, *J* = 8.0 Hz, 2H), 7.68 (d, *J* = 8.0 Hz, 1H), 7.35 (s, 1H), 7.31 (d, *J* = 8.8 Hz, 1H), 6.82 (d, *J* = 8.6 Hz, 1H), 2.79 (br s, 1H), 1.39 (s, 6H), 1.20 (s, 6H); ^{13}C NMR (DMSO-d_6): δ 151.5, 146.0, 140.4, 140.2, 131.1, 129.6, 124.5, 118.2, 116.7, 115.4, 113.7, 63.1, 46.5, 30.2, 22.2; *Anal.* Calcd. for $C_{21}H_{24}N_4O_4$: C, 63.62; H, 6.10; N, 14.13. Found: C, 63.39; H, 6.26; N, 14.27.

1-(1,2,2,4,4-Pentamethyl-3-oxo-1,2,3,4-tetrahydroquinolin-6-yl)-3-(4-(trifluoromethyl)phenyl) urea (**80e**). Yield: 0.28 g (0.67 mmol, 78%) as a brown solid, mp 198-199 ^{o}C; IR (nujol): 3328, 1720, 1656 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 9.01 (s, 1H), 8.61 (s, 1H), 7.63 (q, *J* = 9.3 Hz, 4H), 7.32 (d, *J* = 2.4 Hz, 1H), 7.30 (dd, *J* = 8.5, 2.4 Hz, 1H), 6.80 (d, *J* = 8.6 Hz, 1H), 2.79 (s, 3H), 1.39 (s, 6H), 1.19 (s, 6H); ^{13}C NMR (DMSO-d_6): δ 213.7, 152.1, 141.8, 140.0, 138.7, 131.6, 129.6, 121.1, 119.6 (q, *J* = 255.2 Hz), 118.6, 117.9, 115.2, 113.7, 63.1, 46.5, 30.2, 22.1; *Anal.* Calcd. for $C_{22}H_{24}F_3N_3O_2$: C, 63.00; H, 5.77; N, 10.02. Found: C, 63.12; H, 5.59; N, 10.29.

1-(1,2,2,4,4-Pentamethyl-3-oxo-1,2,3,4-tetrahydroquinolin-6-yl)-3-(4-(trifluoromethoxy)phenyl)urea (**80f**). Yield: 0.27 g (0.62 mmol, 72%) as a brown solid, mp 191-192 ^{o}C; IR (nujol): 3318, 1716, 1648 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 8.78 (s, 1H), 8.52 (s, 1H), 7.54 (d, *J* = 8.5 Hz, 2H), 7.32 (d, *J* = 8.5 Hz, 2H), 7.27-7.25 (m, 3H), 6.79 (d, *J* = 8.6 Hz, 1H), 2.82 (s, 3H), 1.38 (s, 6H), 1.19 (s, 6H); ^{13}C NMR ($CDCl_3$): δ 213.7, 151.8, 143.1, 140.1, 131.4, 129.6, 125.5, 125.4 (q, *J* = 3.5 Hz), 124.0 (q, *J* = 272.4 Hz), 118.1, 117.1, 115.3, 113.7, 63.1, 46.5, 30.2, 22.2; *Anal.* Calcd. for $C_{22}H_{24}F_3N_3O_3$: C, 60.68; H, 5.56; N, 9.65. Found: C, 60.79; H, 5.76; N, 9.83.

General procedure to synthesize 82(a-f). To a stirred solution of **79** (0.2 g, 0.86 mmol) in tetrahydrofuran (10 mL) was added potion-wise lithium aluminum hydride (65.0 mg, 1.72 mmol) at 0 ^{o}C. The reaction was stirred at room temperature for 4 h, quenched with saturated sodium sulfate solution at 0 ^{o}C, filtered through Celite® and washed with ethyl acetate (20 mL). The organic layer was washed with water (20 mL), saturated aqueous NaCl (20 mL), dried (anhydrous Na_2SO_4) and concentrated to give **81** as a brown oil. The residue was dissolved in tetrahydrofuran (5 mL) and added dropwise at room temperature to iso(thio)cyanate **71a-f** (0.86 mmol) in tetrahydrofuran. After TLC analysis indicated the disappearance of **56**, the reaction mixture was

concentrated under vacuum and purified by column chromatography. Concentration of the major fraction and crystallization from dichloromethane/ether mixture (2:8, 7 mL) afforded **82a-f**.

1-(3-Hydroxy-1,2,2,4,4-pentamethyl-1,2,3,4-tetrahydroquinolin-6-yl)-3-(4-nitrophenyl)thiourea (**82a**). Yield: 0.22 g (0.53 mmol, 62%) as a yellow solid, mp 161-163 ^{o}C; IR (nujol): 3444, 1645, 1377 cm^{-1}; ^{1}H NMR (DMSO-d$_6$): δ 10.01 (s, 1H), 10.02 (s, 1H), 8.17 (d, *J* = 8.7 Hz, 2H), 7.81 (d, *J* = 8.7 Hz, 2H), 7.23 (s, 1H), 7.13 (d, *J* = 8.7 Hz, 1H), 6.54 (d, *J* = 8.8 Hz, 1H), 5.21 (d, *J* = 6.3 Hz, 1H), 3.23 (d, *J* = 6.4 Hz, 1H), 2.74 (s, 3H),1.25 (s, 6H), 1.15 (s, 3H), 1.09 (s, 3H); ^{13}C NMR (DMSO-d$_6$): δ 177.9, 146.0, 141.4, 141.3, 131.5, 127.4, 123.7, 122.2, 121.3, 120.5, 110.9, 77.9, 57.9, 37.1, 31.0, 28.5, 26.8, 22.9, 17.9; *Anal.* Calcd. for $C_{21}H_{26}N_4O_3S$: C, 60.85; H, 6.32; N, 13.52. Found: C, 60.58; H, 6.42; N, 13.71.

1-(3-Hydroxy-1,2,2,4,4-pentamethyl-1,2,3,4-tetrahydroquinolin-6-yl)-3-(4-(trifluoromethyl)phenyl)thiourea (**82b**). Yield: 0.23 g (0.52 mmol, 60%) as a brown solid, mp 105-107 ^{o}C; IR: 3345, 1615, 1501, 1067 cm^{-1}; ^{1}H NMR (DMSO-d$_6$): δ 9.79 (s, 2H), 7.73 (d, *J* = 8.5 Hz, 2H), 7.64 (d, *J* = 8.5 Hz, 2H), 7.20 (s, 1H), 7.11 (d, *J* = 8.7 Hz, 1H), 6.53 (d, *J* = 8.7 Hz, 1H), 5.20 (d, *J* = 6.4 Hz, 1H), 3.23 (d, *J* = 6.4 Hz, 1H), 2.74 (s, 3H), 1.25 (s, 3H), 1.24 (s, 3H), 1.15 (s, 3H), 1.09 (s, 3H); ^{13}C NMR (DMSO-d$_6$): δ 178.4, 143.1, 141.3, 131.5, 127.6, 124.8 (q, *J* = 3.6 Hz), 123.9 (q, *J* = 252.2 Hz), 122.4, 121.9, 121.5, 110.9, 77.9, 57.9, 37.1, 31.0, 28.5, 26.8, 22.9, 17.8; *Anal.* Calcd. for $C_{22}H_{26}F_3N_3OS$: C, 60.39; H, 5.99; N, 9.60. Found: C, 60.28; H, 6.12; N, 9.47.

1-(3-Hydroxy-1,2,2,4,4-pentamethyl-1,2,3,4-tetrahydroquinolin-6-yl)-3-(4-(trifluoromethoxy)phenyl)thiourea (**82c**). Yield: 0.24 g (0.52 mmol, 60%) as a brown solid, mp 97-99 ^{o}C; IR: 3419, 1605, 1501, 1376 cm^{-1}; ^{1}H NMR (DMSO-d$_6$): δ 9.62 (s, 1H), 9.55 (s, 1H), 7.57 (d, *J* = 8.6 Hz, 2H), 7.29 (d, *J* = 8.5 Hz, 2H), 7.17 (s, 1H), 7.08 (d, *J* = 8.5 Hz, 1H), 6.52 (d, *J* = 8.8 Hz, 1H), 5.19 (d, *J* = 6.4 Hz, 1H), 3.22 (d, *J* = 6.4 Hz, 1H), 2.73 (s, 3H), 1.25 (s, 3H), 1.24 (s, 3H), 1.14 (s, 3H), 1.09 (s, 3H); ^{13}C NMR (DMSO-d$_6$): δ 179.82, 144.75, 142.35, 139.50,

132.59, 128.69, 125.49, 123.65, 122.74, 121.46, 121.33 (q, *J* = 255.5 Hz), 112.01, 79.02, 58.93, 38.21, 32.03, 29.57, 27.82, 23.94, 18.92; *Anal.* Calcd. for $C_{22}H_{26}F_3N_3O_2S$: C, 58.26; H, 5.78; N, 9.27. Found: C, 58.34; H, 5.57; N, 9.31.

1-(3-Hydroxy-1,2,2,4,4-pentamethyl-1,2,3,4-tetrahydroquinolin-6-yl)-3-(4-nitrophenyl)urea (**82d**). Yield: 0.27 g (0.69 mmol, 80%) as a yellow solid, mp 215-217 °C; IR: 3473, 3251, 1659, 1556 cm^{-1}; ^1H NMR (DMSO-d_6): δ 9.27 (s, 1H), 8.51 (s, 1H), 8.17 (d, *J* = 8.7 Hz, 2H), 7.67 (d, *J* = 8.8 Hz, 2H), 7.27 (s, 1H), 7.11 (d, *J* = 8.6 Hz, 1H), 6.51 (d, *J* = 8.8 Hz, 1H), 5.17 (d, *J* = 6.4 Hz, 1H), 3.23 (d, *J* = 6.4 Hz, 1H), 2.71 (s, 3H), 1.26 (s, 3H), 1.23 (s, 3H), 1.16 (s, 3H), 1.06 (s, 3H); ^{13}C NMR (DMSO-d_6): δ 151.5, 146.2, 140.0, 139.8, 132.1, 128.0, 124.5, 117.9, 117.1, 116.5, 111.4, 78.2, 57.7, 37.2, 30.9, 28.8, 26.5, 22.9, 17.6; *Anal.* Calcd. for $C_{21}H_{26}N_4O_4$: C, 63.30; H, 6.58; N, 14.06. Found: C, 63.62; H, 6.81; N, 14.16.

1-(3-Hydroxy-1,2,2,4,4-pentamethyl-1,2,3,4-tetrahydroquinolin-6-yl)-3-(4-(trifluoromethyl)phenyl)urea (**82e**). Yield: 0.26 g (0.61 mmol, 71%) as a brown solid; mp 213-215 °C; IR: 3308, 1647, 1605 cm^{-1}; ^1H NMR (DMSO-d_6): δ 8.92 (s, 1H), 8.38 (s, 1H), 7.64 (d, *J* = 8.7 Hz, 2H), 7.60 (d, *J* = 8.7 Hz, 2H), 7.25 (d, *J* = 2.3 Hz, 1H), 7.10 (dd, *J* = 8.7, 2.3 Hz, 1H), 6.50 (d, *J* = 8.7 Hz, 1H), 5.16 (d, *J* = 6.4 Hz, 1H), 3.22 (d, *J* = 6.4 Hz, 1H), 2.70 (s, 3H), 1.26 (s, 3H), 1.22 (s, 3H), 1.16 (s, 3H), 1.06 (s, 3H); ^{13}C NMR (DMSO-d_6): δ 151.9, 143.3, 139.6, 132.1, 128.4, 125.4 (q, *J* = 4.4 Hz), 124.6 (q, *J* = 265.5 Hz), 117.7, 117.0, 116.9, 111.4, 78.2, 57.7, 37.2, 30.9, 28.8, 26.5, 22.9, 17.6; *Anal.* Calcd. for $C_{22}H_{26}F_3N_3O_2$: C, 62.70; H, 6.22; N, 9.97. Found: C, 62.58; H, 6.48; N, 10.12.

1-(3-Hydroxy-1,2,2,4,4-pentamethyl-1,2,3,4-tetrahydroquinolin-6-yl)-3-(4-(trifluoromethoxy)phenyl)urea (**82f**). Yield: 0.25 g (0.57 mmol, 66%) as a brown solid, mp 188-189 °C; IR: 3467, 3310, 1648, 1554 cm^{-1}; ^1H NMR (DMSO-d_6): δ 8.68 (s, 1H), 8.28 (s, 1H), 7.53 (d, *J* = 8.7 Hz, 2H), 7.26 (s, 1H), 7.23 (d, *J* = 8.7 Hz, 1H), 7.09 (dd, *J* = 8.7, 2.5 Hz, 1H), 6.49 (d, *J* = 8.8 Hz, 1H), 5.16 (d, *J* = 6.4 Hz, 1H), 3.32 (s, 3H), 3.22 (d, *J* = 6.4 Hz, 1H) 2.70 (s,

3H), 1.26 (s, 3H), 1.22 (s, 3H), 1.16 (s, 3H), 1.05 (s, 3H); ^{13}C NMR (DMSO-d_6): δ 152.2, 139.5, 138.9, 132.1, 128.7, 121.0, 119.6 (q, J = 255.1 Hz), 118.5, 117.7, 117.0, 111.5, 78.2, 57.7, 37.2, 30.9, 28.8, 26.5, 22.9, 17.5; *Anal.* Calcd. for $C_{22}H_{26}F_3N_3O_3$: C, 60.40; H, 5.99; N, 9.61. Found: C, 60.28; H, 6.15; N, 9.38.

1.6.5 Tethering bioactive molecules to S-Het-A2 rings

General methods: Commercial anhydrous *N*,*N*-dimethylformamide was stored under dry N_2 and transferred by syringe into reactions when needed. Tetrahydrofuran was dried over potassium hydroxide pellets and distilled from lithium aluminum hydride prior to use. All other commercial reagents and solvents were used as received. Unless otherwise indicated, all reactions were carried out under dry N_2 in oven-dried glassware. Reactions were monitored by thin layer chromatography (TLC, Analtech No 21521) using silica gel GF plates. Preparative separations were performed by column chromatography on silica gel (Davisil®, grade 62, 60-200 mesh) containing UV-active phosphor (Sorbent Technologies No UV-05) slurry packed into quartz columns. Band elution for all chromatographic separations was monitored using a hand-held UV lamp. Melting points were uncorrected. IR spectra were run as chloroform solutions on NaCl disks or in nujol. The ^{1}H- and ^{13}C-NMR spectra were measured in the indicated solvent at 400 MHz and 100 MHz, respectively, using tetramethylsilane as the internal standard with coupling constants (*J*) given in Hz.

General methods to synthesize 84(a,b), 86(a,b), 88(a,b) and 91. To a stirred solution of the corresponding amino compound (0.5 mmol) in tetrahydrofuran (5 mL), was added iso(thio)cyanates **71a, 71d, 90** (0.5 mmol) in tetrahydrofuran (2 mL) dropwise at room temperature under nitrogen atmosphere. The reactions were stirred until TLC analysis indicated complete conversion of the amino compound. The solvent was evaporated under vacuum and each product was purified by column chromatography. The eluted products were stirred with ether/pentane (3:7) to afford the crystalline urea or thiourea derivatives.

1-(4-Nitrophenyl)-3-(quinolin-6-yl)urea (**84a**). Yield: 142 mg (0.46 mmol, 92%) as a yellow solid, mp 266-267 ^{o}C; IR: 3404, 1716, 1620, 1573, 1374 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 9.56 (s, 1H), 9.29 (s, 1H), 8.77 (d, *J* = 2.3 Hz, 1H), 8.29 (d, *J* = 8.4 Hz, 1H), 8.22 (d, *J* = 8.7 Hz, 3H), 7.98 (d, *J* = 8.7 Hz, 1H), 7.74 (d, *J* = 8.8 Hz, 3H), 7.49 (dd, *J* = 6.5, 1.4 Hz, 1H); ^{13}C NMR (DMSO-d_6): δ 152.5, 149.1, 146.7, 144.8, 141.6, 137.5, 135.7, 130.1, 128.9, 125.6, 123.5, 118.1, 114.25; *Anal*. Calcd. for $C_{16}H_{12}N_4O_3$: C, 62.33; H, 3.92; N, 18.17. Found: C, 62.18; H, 3.74; N, 17.98.

1-(4-Nitrophenyl)-3-(quinolin-6-yl)thiourea (**84b**). Yield: 144 mg (0.44 mmol, 89%) as a yellow solid, mp 172-173 ^{o}C; IR: 3144, 1594, 1563, 1496, 1336 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 10.55 (d, *J* = 13.1 Hz, 2H), 8.85 (d, *J* = 4.1 Hz, 1H), 8.34 (d, *J* = 8.3 Hz, 1H), 8.23 (d, *J* = 8.9 Hz, 3H), 8.11 (s, 1H), 8.0 (d, *J* = 9.0 Hz, 1H), 7.89-7.85 (m, 3H), 7.52 (dd, *J* = 8.2, 4.1 Hz, 1H); ^{13}C NMR (DMSO-d_6): δ 180.1, 150.3, 146.6, 145.9, 142.9, 137.5, 136.1, 129.6, 128.5, 124.9, 122.3, 122.2, 120.8; *Anal*. Calcd. for $C_{16}H_{12}N_4O_2S$: C, 59.25; H, 3.73; N, 17.27. Found: C, 59.18; H, 3.76; N, 17.48.

1-(1*H*-Indol-5-yl)-3-(4-nitrophenyl)urea (**86a**). Yield: 141 mg (0.48 mmol, 95%) as a yellow solid, mp 243-244 ^{o}C; IR: 3329, 1685, 1636, 1598, 1567, 1375 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 10.99 (s, 1H), 9.35 (s, 1H), 8.66 (s, 1H), 8.18 (d, *J* = 8.8 Hz, 2H), 7.70-7.68 (m, 3H), 7.32 (d, *J* = 8.5 Hz, 2H), 7.10 (d, *J* = 8.7 Hz, 1H), 6.37 (s, 1H); ^{13}C NMR (DMSO-d_6): δ 152.7, 147.3, 141.1, 133.1, 131.1, 128,1, 126.4, 125.6, 117.7, 115.4, 111.8, 111.0, 101.4; *Anal*. Calcd. for $C_{15}H_{12}N_4O_3$: C, 60.81; H, 4.08; N, 18.91. Found: C, 60.63; H, 4.12; N, 19.04.

1-(1*H*-Indol-5-yl)-3-(4-nitrophenyl)thiourea (**86b**). Yield: 140 mg (0.45 mmol, 90%) as a yellow solid, mp 171-172 ^{o}C; IR: 3451, 3421, 1586, 1512, 1375 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 11.14 (s, 1H), 10.18 (s, 1H), 10.12 (s, 1H), 8.18 (d, *J* = 8.6 Hz, 2H), 7.86 (d, *J* = 8.6 Hz, 2H), 7.58 (s, 1H), 7.40 (s, 1H), 7.37 (s, 1H), 7.09 (d, *J* = 8.8 Hz, 1H), 6.44 (s, 1H); ^{13}C NMR (DMSO-d_6): δ 179.9, 147.2, 142.5, 134.5, 130.7, 128.1, 126.7, 124.7, 122.0, 119.6, 116.7, 111.9, 101.8; *Anal*. Calcd. for $C_{15}H_{12}N_4O_2S$: C, 57.68; H, 3.87; N, 17.94. Found: C, 57.82; H, 3.92; N, 18.04.

1-(Benzo[d]oxazol-6-yl)-3-(4-nitrophenyl)urea (88a). Yield: 142 mg (0.48 mmol, 95%) as a brown solid, mp 255-257 °C; IR: 3356, 3269, 1654, 1556, 1335 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 9.51 (s, 1H), 9.22 (s, 1H), 8.65 (s, 1H), 8.21 (d, *J* = 8.8 Hz, 2H), 8.09 (s, 1H), 7.72 (d, *J* = 8.5 Hz, 3H), 7.31 (d, *J* = 8.7 Hz, 1H); ^{13}C NMR (DMSO-d_6): δ 154.1, 152.5, 150.2, 146.7, 141.6, 137.6, 135.2, 125.6, 120.4, 118.0, 116.7, 101.5; *Anal*. Calcd. for $C_{14}H_{10}N_4O_4$: C, 56.38; H, 3.38; N, 18.79. Found: C, 56.45; H, 3.11; N, 18.94.

1-(Benzo[d]oxazol-6-yl)-3-(4-nitrophenyl)thiourea (88b). Yield: 141 mg (0.45 mmol, 90%) as a yellow solid, mp 166-167 °C; IR: 3147, 1596, 1553, 1374 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 10.45 (d, *J* = 6.8 Hz, 2H), 8.74 (s, 1H), 8.22 (d, *J* = 8.8 Hz, 2H), 8.04 (s, 1H), 7.85 (d, *J* = 8.9 Hz, 2H), 7.78 (d, *J* = 8.5 Hz, 1H), 7.41 (d, *J* = 8.7 Hz, 1H); ^{13}C NMR (DMSO-d_6): δ 179.1, 154.0, 148.6, 145.6, 141.8, 136.3, 136.1, 123.8, 121.2, 120.8, 119.1, 106.3; *Anal*. Calcd. for $C_{14}H_{10}N_4O_3S$: C, 53.50; H, 3.21; N, 17.83. Found: C, 53.67; H, 3.43; N, 18.10.

1-(Furan-2-ylmethyl)-3-(2,2,4,4-tetramethylthiochroman-6-yl)thiourea (91). Yield: 148 mg (0.41 mmol, 82%) as a yellow solid; mp 164-166 °C; IR: 3386, 1532, 1475 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ (ppm) 7.61 (s, 1H), 7.33 (dd, *J* = 1.7, 0.8 Hz, 2H), 7.21 (d, *J* = 2.3 Hz, 1H), 7.15 (d, *J* = 8.3 Hz, 1H), 6.32-6.31 (m, 1H), 6.28 (dd, *J* = 3.2, 0.6 Hz, 3H), 6.21 (t, *J* = 5.3 Hz, 1H), 4.85 (d, *J* = 5.2 Hz, 1H), 1.94 (s, 2H), 1.42 (s, 6H), 1.33 (s, 6H); ^{13}C NMR (DMSO-d_6): δ 180.5, 150.2, 144.8, 142.4, 132.8, 132.4, 129.5, 124.1, 122.9, 110.5, 108.2, 53.8, 42.5, 42.3, 35.8, 32.5, 31.6; *Anal*. Calcd. for $C_{19}H_{24}N_2OS_2$: C, 63.30; H, 6.71; N, 7.77. Found: C, 63.47; H, 6.53; N, 7.89.

2-((2,2,4,4-Tetramethylthiochroman-6-yl)carbamoyl)phenyl acetate (93). To a stirred solution of acetyl salicylic acid **92** (90 mg, 0.5 mmol) in *N*,*N*-dimethylformamide (5 mL) was added DIPEA (261 µL, 1.5 mmol), EDC.HCl (105 mg, 0.55 mmol), and HOBt (74 mg, 0.55 mmol). After stirring for 1 h at room temperature, **89** (110 mg, 0.5 mmol) in *N*,*N*-dimethylformamide (2 mL) was added dropwise. The resulting mixture was stirred at room temperature for 12 h. The

reaction mixture was poured into ice (approx. 50 g) and was stirred for 30 min. The aqueous layer was then extracted with ethyl acetate (3 x 100 mL). The combined organic layers were washed with saturated aqueous NaCl (2 x 50 mL), dried ($MgSO_4$), and concentrated under vacuum to afford the corresponding crude amide **93.** It was purified by silica gel column chromatography eluted with hexanes:ethyl acetate (1:1) to afford the pure amide **93** (167 mg, 0.43 mmol, 87%) as a white solid; mp 130-132 ^oC; IR: 3307, 1767, 1659, 1525 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.96 (s, 1H), 7.86 (dd, *J* = 7.9, 1.8 Hz, 1H), 7.73 (d, *J* = 2.3 Hz, 1H), 7.52 (td, *J* = 7.9, 1.8 Hz, 1H), 7.37 (t, *J* = 7.6 Hz, 1H), 7.26 (dd, *J* = 8.0, 2.5 Hz, 1H), 7.16 (dd, *J* = 8.0, 2.5 Hz, 1H), 7.12 (d, *J* = 8.4 Hz, 1H), 2.35 (s, 3H), 1.96 (s, 2H), 1.42 (s, 6H), 1.41 (s, 6H); ^{13}C NMR ($CDCl_3$): δ 169.3, 163.5, 147.8, 143.7, 135.1, 132.1, 129.9, 128.8, 128.6, 126.6, 123.3, 118.6, 118.1, 54.3, 42.2, 35.8, 32.5, 31.6, 21.1; *Anal*. Calcd. for $C_{22}H_{25}NO_3S$ C, 68.90; H, 6.57; N, 3.65. Found: C, 69.13; H, 6.23; N, 3.31.

1-(4-Aminophenyl)-3-(2,2,4,4-tetramethylthiochroman-6-yl)thiourea (**95**). To a stirred solution of S-Het-A2 (0.45 g, 1.3 mmol) and iron powder (0.39 g, 7.02 mmol) in an ethanol:water mixture (4:1, 20 mL) was added NH_4Cl (0.14 g, 2.6 mmol), and the resulting mixture was refluxed for 4 h. The reaction mass was cooled to room temperature and filtered through a bed of Celite®. The Celite® was washed with ethanol (3 x 20 mL), and the solution was concentrated under vacuum at 45 ^oC to give a yellow solid. The crude product was purified by silica gel column chromatography eluted with dichloromethane:ethyl acetate (7:3) to afford **95** (0.46 g, 1.23 mmol, 95%) as a yellow solid, mp 156-157 ^oC; IR: 3309, 3190, 1334 cm^{-1}; ^1H NMR ($CDCl_3$): δ 8.21 (d, *J* = 8.7 Hz, 2H), 8.03 (s, 1H), 7.80 (s, 1H), 7.75 (d, *J* = 8.7 Hz, 2H), 7.32 (s, 1H), 7.22 (d, *J* = 8.3 Hz, 1H), 7.02 (d, *J* = 8.3 Hz, 1H), 1.98 (s, 2H), 1.45 (s, 6H), 1.40 (s, 6H); ^{13}C NMR ($CDCl_3$): δ 179.0, 145.2, 144.6, 143.9, 134.2, 132.0, 129.7, 124.6, 124.2, 123.1, 122.9, 53.7, 42.5, 35.9, 32.5, 31.6. *Anal*. Calcd for $C_{20}H_{25}N_3S_2$: C, 64.65; H, 6.78; N, 11.31. Found: C, 64.81; H, 6.98; N, 11.42.

CHAPTER II

METAL FREE SYNTHETIC APPROACHES TO BIOACTIVE MOLECULES

2.1 Introduction

In recent years, the use of transition metals has dominated organic synthesis to a greater extent. This overuse of rare metals in organic reactions, would result in depletion of natural resources as

well as generation of more toxic waste that could destroy the environment for future generations. Though transition metals have helped to achieve some useful transformations that were impossible 50 years ago, our work has cast doubt on the necessity of metals in certain organic reactions these catalysts often require special purification technique to remove them from products as well. Viable alternatives that could minimize or avoid the usage of metals catalysts are needed to protect reserves of precious metals and to simplify purification procedures. Improvement in the synthetic methodology attempted on sildenafil citrate is noteworthy. Sildenafil citrate is an active ingredient in Viagra™ and Revatio™. Viagra™ needs no introduction, in its first year on the market it achieved sales of $1 billion.[50] Revatio™ is an important medicine to treat pulmonary hypertension in adults and children. The alternative strategy of developing new synthetic routes to avoid tin(II) chloride in the synthesis eliminated 30,000 tons of chemical waste between 1997 and 2003.[51]

Our research group, is involved primarily in synthesizing new drug molecules as anti-cancer and anti-bacterial agents. However, we also have expertise in developing cost effective and atom efficient synthetic approaches to bioactive molecules such as quinolinones, quinazolinones, napthyridinones, chromanes and many others. As a part of this dissertation work, new methods have been developed to prepare isoquinolin-1(2*H*)-ones, 1,6-naphthyridin-5(6*H*)-ones, pyrazoloquinazolinones, pyrazolo- pyridopyrimidinones, benzo[4,5]imidazo[2,1-*b*]quinazolin-12-ones, benzo[4,5]imidazo[1,2-*a*]pyrido[2,3-*d*]pyrimidin-5-ones, 1,3,4-oxadiazoles and 4-chromanones as well as adding nucleophiles across polarized vinyl arenes.

These methods were developed in an economically viable and atom efficient manner thereby providing an alternative strategy to access these bioactive motifs without using metals in the reaction procedure. Adopting these methods will definitely reduce the chemical waste to a greater extent and also simplify the isolation process. Initially, we adopted the nucleophilic aromatic substitution reaction (S_NAr) strategy to prepare isoquinolin-1(2*H*)-ones in an excellent yield.

Encouraged by this result, we extended the method to prepare pyrazoloquinazolinones, pyrazolo-pyridopyrimidinones, benzo[4,5]imidazo[2,1-*b*]quinazolin-12-ones and benzo[4,5]imidazo[1,2-*a*]pyrido[2,3-*d*]pyrimidin-5-ones.

The S_NAr reaction is a nucleophilic aromatic substitution proceeding *via* an addition-elimination mechanism. It has been known for more than 150 years, and its importance can be understood by its wide application in organic synthesis and industry.[52] In this type of reaction, most commonly a halogen on an electron deficient arene is replaced by a nucleophile. For a nucleophilic aromatic substitution reaction to occur, electron-withdrawing groups must be positioned ortho or para to the halogen. The greater the number of electron-withdrawing substituents, the more easily the nucleophilic aromatic substitution takes place (Figure 2.1).

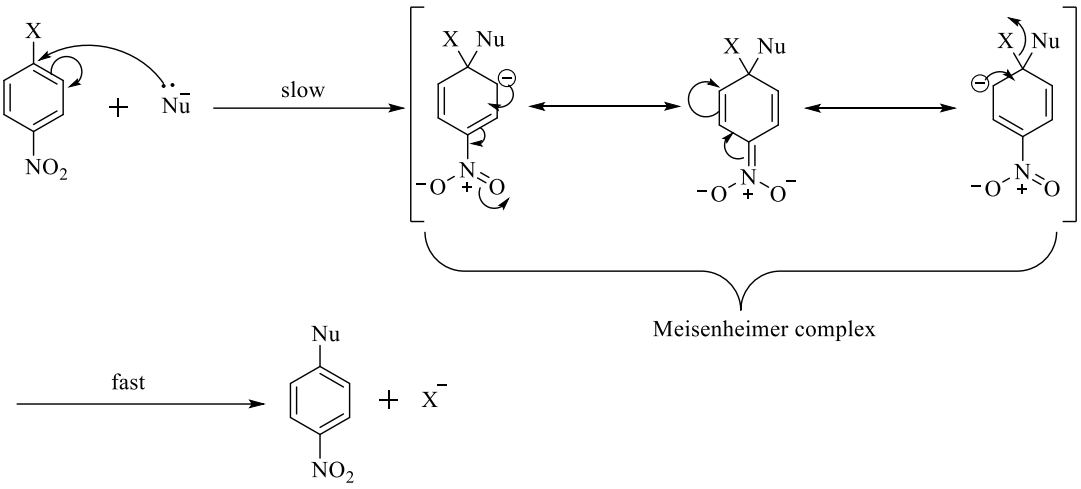


Figure 2.1. General Mechanism for S_NAr reaction

A general mechanism for the S_NAr reaction is depicted in Figure 2.1. It is a two-step process. The first step is the slow step and involves nucleophilic attack on the carbon bearing the halogen to form a resonance-stabilized carbanion intermediate called a Meisenheimer complex. The next step is the fast step, the elimination of the halogen to restore aromaticity.[53] The order of reactivity is fluoride > chloride > bromide > iodide.

2.2 Results and Discussion

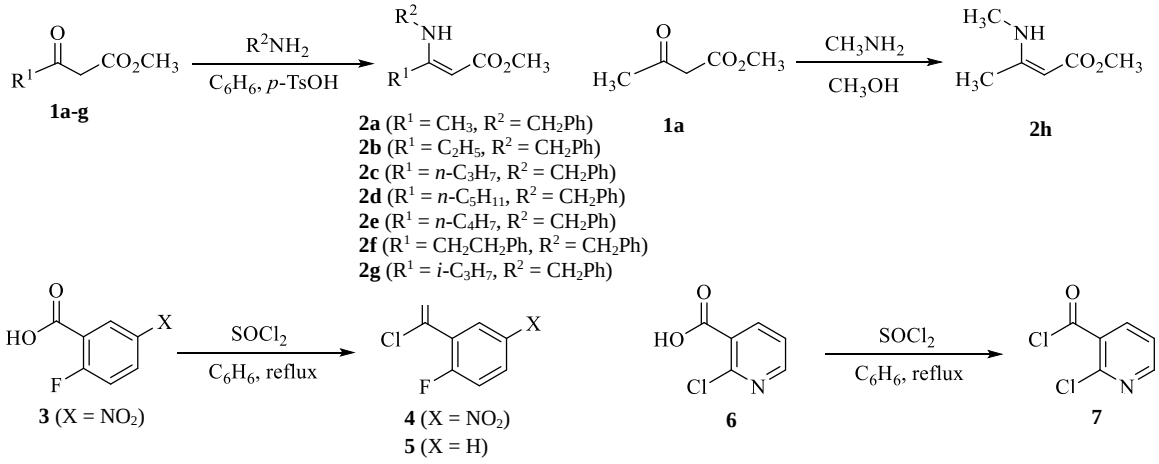
2.2.1 Isoquinolin-1(2*H*)-ones and 1,6-naphthyridin-5(6*H*)-ones

The current study was undertaken with the goal of providing an expeditious route to 2,3-dialkyl-4-methoxycarbonylisoquinolin-1(2*H*)-ones and 6,7-dialkyl-8-methoxycarbonyl-1,6-naphthyridin-5(6*H*)-ones. Several 4-ethoxycarbonylisoquinolin-1(2*H*)-ones have previously been prepared from homophthalic acid[54-58] and 2-bromobenzoic acid derivatives.[59-62] While the syntheses described were reasonably short (2-3 steps), the yields were often quite low (35-50%). These compounds are known to have significant potential for the treatment of ulcers,[63] inflammation-based diseases[64] and CNS disorders.[59, 65] In contrast, 6,7-dialkyl-8-methoxycarbonyl-1,6-naphthyridin-5(6*H*)-ones have been reported only once in 40-50% yields by a route that differs from the current work,[66] and to the best of our knowledge, have not been evaluated for biological activity.

Our synthetic approach is based upon earlier investigations by two groups. Horii and co-workers were the first to demonstrate the use of a tandem enamination-cyclization procedure between ethyl piperidineacetate and cyclohexanone to produce 1,2,3,4,4a,5,7,8,9,10-decahydro-6*H*-benzo[*c*]quinolizin-6-one as a possible azasteroid precursor.[67] Later, the Stille group disclosed a related aza-annulation sequence and applied it to the synthesis of several alkaloid targets.[68-69] This process involved *N*-acylation of a conjugated enaminoester with acryloyl chloride, followed by intramolecular Michael addition of the enamine to the resulting acrylamide. In the current study, we have modified this process to utilize an electron-poor fluoroaromatic moiety to serve as the acceptor for the second stage of this process. This has led to an efficient synthesis of 2,3-dialkyl-4-methoxycarbonylisoquinolin-1(2*H*)-ones and 6,7-dialkyl-8-methoxycarbonyl-1,6-naphthyridin-5(6*H*)-ones. Based on the medicinal properties of previously reported derivatives in the isoquinoline series, this method could lead to new structures worthy of further development.

Appropriate cyclization substrates were readily obtained from commercial sources or by standard synthetic procedures (Scheme 1). β-Ketoesters **1a-g**[70] were converted to β-enaminoesters **2a-g** by

p-TsOH-catalyzed condensation with benzylamine in refluxing benzene with Dean-Stark removal of water. *N*-Methyl-β-enaminoester **2h** was prepared by a literature procedure.[71] Acids **3** and **6** were converted to acid chlorides **4** and **7**, respectively, using thionyl chloride in boiling benzene, while 2-fluorobenzoyl chloride (**5**) was commercially available.



Scheme 2.1. Synthesis of the reaction substrates

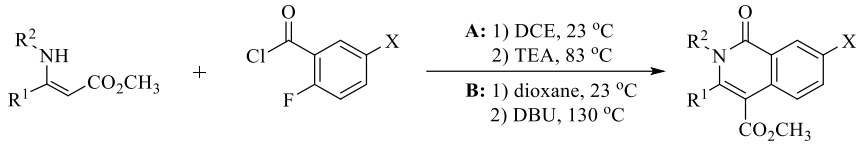
Our cyclization results are summarized in Tables 2.1 and 2.2. The reactions were performed by stirring enaminoesters **2a-h** (2 equiv) with acid chloride **4** (1 equiv) in purified 1,2-dichloroethane (DCE) at 23 °C for 3 h, followed by addition of trimethylamine (TEA, 2 equiv) and heating at reflux for 12-18 h. Our experiments revealed that *N*-acylation of the enaminoester proceeded best at room temperature, while the final S_NAr ring closure required heating. For substrates having a monoactivated aromatic acceptor, such as **5**, reactions were performed similarly in purified 1,4-dioxane[72] using a pressure tube with 1,8-diazabicyclo[5.4.0] undec-7-ene (DBU) as the base (2 equiv, 130 °C, 3 h) for the cyclization. Finally, reactions involving 2-chloronicotinoyl chloride (**7**) were achieved using the enaminoester (3 equiv) in DCE with TEA as the base (2 equiv, 130 °C, 8

h). The use of anhydrous, purified solvents was essential, as the enaminoesters were both water and acid sensitive. Failure to remove these impurities from DCE and dioxane resulted in hydrolysis of the enamine to give benzylamine, which readily added to the S_NAr acceptor ring, preempting the ring closure. The reaction was facilitated by the use of excess enamine. While TEA or DBU were found to be the best reagents for promoting the final cyclization, the use of these bases (or elevated temperatures) for the initial acylation had a negative impact on the overall yields. Upon completion, the crude reaction mixtures were added to aqueous NaCl and subjected to an extractive work-up. Purification was accomplished by chromatography followed by recrystallization.

Some further discussion is warranted regarding the use of excess enaminoester **2** for these transformations. In heterocyclizations involving **4** and **5**, 2 equiv of this reactant were necessary, with the second equivalent neutralizing the HCl produced during the acylation step. For reactions of 2-chloronicotinoyl chloride (**7**), however, it was found that 3 equiv of **2** were required for optimum conversion rather than two. This stems from the fact that **7** incorporates an extra equivalent of HCl due to the basic nitrogen of the pyridine, and this acid could sabotage the reaction sequence at several stages. Protonation at nitrogen significantly increases the C2 reactivity of 2-chloropyridines toward nucleophiles,[73] and thus, attack at this site could compete with the acylation process. Additionally, the 2-chloropyridinium cation could serve as a proton source [pK_a ~ 0.48 (H_2O)][74] to deactivate the enaminoester nitrogen or protonate the enamide double bond. Hence, it was important to neutralize this salt in addition to the HCl produced during enamide formation to decrease the probability of side reactions. This was most effectively accomplished by addition of **7** to a cooled solution containing 3 equiv of **2**. The alternative use of bases, such as TEA or DBU during the acylation stage, was found to lower the overall product yields. Inorganic bases were not explored since reaction of these with HCl would produce water, which could degrade both reactants. The delocalized enaminoesters have base properties

intermediate between 2-chloropyridine and TEA and scavenge the acid without introducing additional contaminants. They are easily prepared from inexpensive commercial chemicals and do not require purification prior to reaction. Moreover, in applications where the precursor ketoester is costly or demands independent synthesis, the required use of surplus **2** is mitigated by the fact that much of this material can be recovered as the ketoester and recycled.

Table 2.1 Cyclization results for 2,3-dialkyl-4-methoxycarbonylisoquinolin-(2*H*)-ones

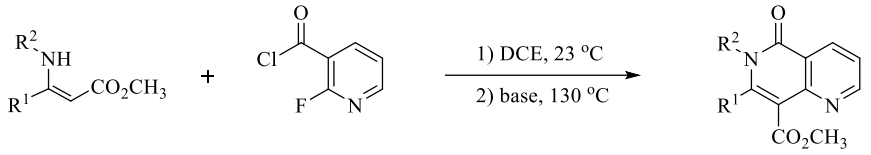


2a-h + **4** (X = NO_2), **5** (X = H) → **8a-h** (X = NO_2), **9a-h** (X = H)

Entry	R^1	R^2	X	Conds	Pdt	Yield (%)
a	CH_3	CH_2Ph	NO_2	A	**8a**	86
b	C_2H_5	CH_2Ph	NO_2	A	**8b**	85
c	*n*-C_3H_7	CH_2Ph	NO_2	A	**8c**	77
d	*n*-C_5H_{11}	CH_2Ph	NO_2	A	**8d**	74
e	3-butenyl	CH_2Ph	NO_2	A	**8e**	68
f	CH_2CH_2Ph	CH_2Ph	NO_2	A	**8f**	81
g	*i*-C_3H_7	CH_2Ph	NO_2	A	**8g**	30
h	CH_3	CH_3	NO_2	A	**8h**	85
a	CH_3	CH_2Ph	H	B	**9a**	57
b	C_2H_5	CH_2Ph	H	B	**9b**	52
c	*n*-C_3H_7	CH_2Ph	H	B	**9c**	58
d	*n*-C_5H_{11}	CH_2Ph	H	B	**9d**	50
e	3-butenyl	CH_2Ph	H	B	**9e**	60
f	CH_2CH_2Ph	CH_2Ph	H	B	**9f**	73
g	*i*-C_3H_7	CH_2Ph	H	B	**9g**	30

h	CH_3	CH_3	H	B	**9h**	53

Table 2.2 Cyclization results for 6,7-dialkyl-8-methoxycarbonyl-1,6-naphthyridin-5(6*H*)-ones

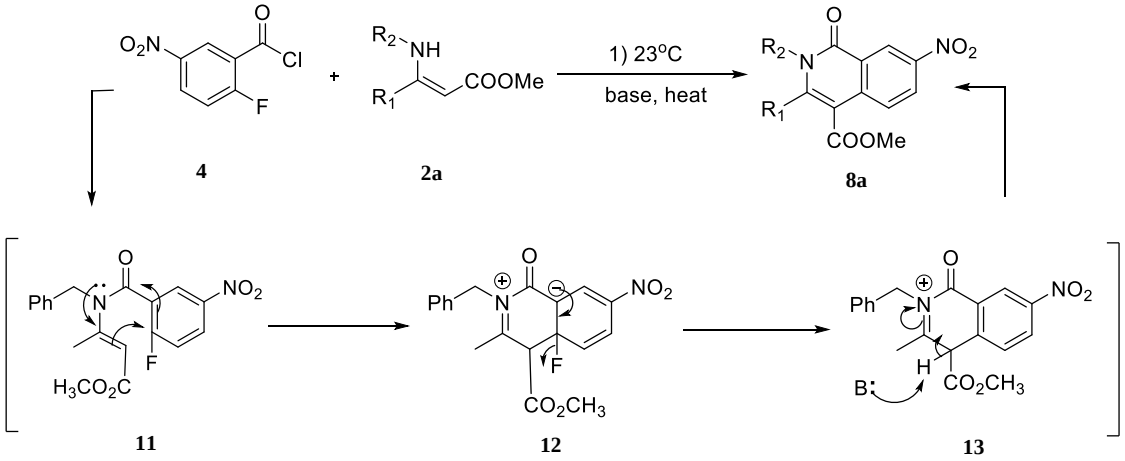


2a-h **7** **10a-h**

Entry	R^1	R^2	Pdt	TEA Yield (%)	DBU Yield (%)
a	CH_3	CH_2Ph	**10a**	70	59
b	C_2H_5	CH_2Ph	**10b**	74	62
c	*n*-C_3H_7	CH_2Ph	**10c**	76	68
d	*n*-C_5H_{11}	CH_2Ph	**10d**	70	52
e	3-butenyl	CH_2Ph	**10e**	70	61
f	CH_2CH_2Ph	CH_2Ph	**10f**	72	60
g	*i*-C_3H_7	CH_2Ph	**10g**	0	0
h	CH_3	CH_3	**10h**	84	78

As expected, cyclizations on aromatic acceptors with two electron-withdrawing groups or a 2-chloropyridine generally proceeded in higher yields and under milder conditions. Monoactivated substrates required a stronger base and more robust thermal conditions. The sequence proved limited with respect to the steric environment adjacent to the nucleophilic enamine carbon. For example, branching at the α-carbon of R^1, as in **2g**, reduced the yields from mono- and diactivated substrates and completely suppressed cyclization for heteroaromatic systems. In these cases,

degradation of the acylated enamine, presumably through elimination of the halogen from the acceptor ring, competed with cyclization. Substrates having straight-chain alkyl groups at R^1, however, cyclized in good to excellent yields for all aromatic acceptors investigated, making this a viable approach to these highly functionalized heterocycles. Though most of our work was done using the *N*-benzyl-β-enaminoesters (e.g., R^2 = benzyl), two reactions with the *N*-methyl derivative **2h** were equally successful. Thus, variation of both R^1 and R^2 can be used to introduce substituent diversity to these systems.



Scheme 2.2. Presumed mechanism for the formation of **8a**

A possible mechanism is illustrated in Scheme 2.2 for the reaction of **2a** with **4**. In the initial step, the enaminoester **2a** is *N*-acylated by acid chloride **4** to give **11**. This would be followed by attack of the *N*-acyl-β-enaminoester on the aromatic acceptor to generate the fused ring system **12**. Rearomatization, with loss of fluoride, would then give the 2,3-dialkyl-4-methoxycarbonyl-7-nitroisoquinolinium-1(4*H*)-one intermediate **13**. In the final step, base (TEA or DBU) would remove the acidic proton from the ester-substituted benzylic carbon to convert **13** to the final product **8a**.

2.2.2 Conclusion

In conclusion, we have developed a practical and efficient approach for the synthesis of 2,3-dialkyl-4-methoxycarbonylisoquinoline-1(2*H*)-one and 6,7-dialkyl-8-methoxycarbonyl-1,6-

naphthyridin-5(6*H*)-ones using a sequential *N*-acylation-S_NAr process. The method involved room temperature *N*-acylation of readily available enaminoesters **2a-h** with 2-fluoro-5-nitrobenzoyl chloride, 2-fluorobenzoyl chloride, and 2-chloronicotinoyl chloride followed by heating to promote the final S_NAr ring closure. Yields were generally in the 52-86% range. The reaction proceeded smoothly for mono- and diactivated aromatic acceptor rings as well as 2-chloropyridine systems but manifested steric limitations in the ring-forming step when a-branched alkyl groups were positioned adjacent to the nucleophilic enamine carbon.

2.2.3 Pyrazoloquinazolinones and pyrazolopyridopyrimidinones

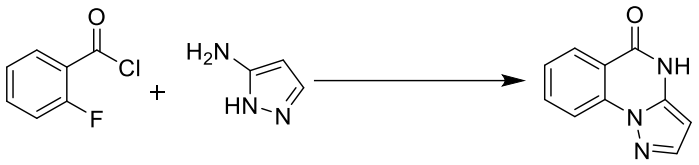
This work describes the application of an earlier protocol to the synthesis of pyrazolo[1,5-*a*]quinazolin-5(4*H*)-ones and pyrazolo[1,5-*a*]-pyrido[3,2-*e*]pyrimidin-5(4*H*)-ones. Our literature search revealed that few methods are available for the synthesis of these heterocycles, and most entail multistep procedures. The earliest approach, reported by Michaelis[2] involved a four-step synthesis of 5*H*-benzo[*d*]pyrazolo[5,1-*b*][1,3]oxazin-5-one followed by heating with aqueous ammonia under pressure. Nearly 60 years later, Wright[75] reported a second approach from substituted 2-hydrazinobenzoic acids and unsaturated nitriles, a method that has been further modified to proceed under microwave conditions.[76] A third synthesis, designed to give the 2-amino-4-methyl derivatives, required the preparation of 2-(3-methyl-4-oxo-3,4-dihydroquinazolin-2-yl)acetonitrile,[77-78] followed by a three-step conversion to the target. Thus, a need exists to develop a more efficient approach to the synthesis of these systems.

Our study began by focusing on the reaction of 2-fluorobenzoyl chloride (**5**) with 5-amino-1*H*-pyrazole (**14a**) to give **15a**. This transformation should permit assessment of the viability of this approach to the target compounds and optimization of the process. The reaction was initially attempted by acylation of the pyrazole (1.3 equiv) with the acid chloride (1 equiv) at 23 ^oC in the presence of 3.0 equiv of triethylamine in 1,2-dichloroethane (DCE). Subsequent heating at 84 ^oC resulted in *ca*. 15% conversion to the heterocycle with numerous side products. To better control

the initial acylation, we performed this step at 10 °C in DMSO containing 3.0 equiv of K_2CO_3 and obtained cleaner formation of the monoacylated product. We then proceeded to optimize the conditions for the final S_NAr cyclization and found that direct heating of this mixture at 150 °C for 30 min gave complete conversion to the pyrazoloquinazolinone.

Using this procedure, isolation of the heterocycle proved troublesome as it was only sparingly soluble in common organic solvents, and DMSO (bp 189 °C) was difficult to remove under vacuum. Thus, only 45% of the product was isolated in pure form using this solvent. Other media, such as dichloroethane (DCE), acetonitrile (ACN) and tetrahydrofuran (THF) were found to be unsatisfactory due to solubility problems and low boiling points. Finally, the entire sequence was repeated in DMF (bp 153 °C), the solvent was removed by rotary evaporation, and the yield was improved to 81%. Further refinement of the conditions revealed that 2.0 equiv of K_2CO_3 was sufficient to promote product formation, while < 2 equiv dramatically lowered the yield (see Table 2.3). Similar results were observed when 2-fluoro-5-nitrobenzoyl chloride and 2-chloronicotinoyl chloride were used as substrates.

Table 2.3. Reaction optimization results for **15a**



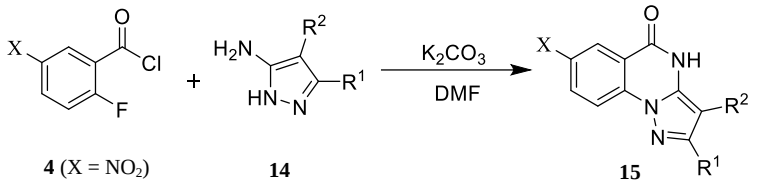
5 **14a** **15a**

Entry	Base	Equiv	*T* (ºC)	Solvent	% Yield
1	TEA	3.0	84	DCE	15
2	DBU	3.0	84	DCE	20
3	Na_2CO_3	3.0	150	DMSO	35
4	K_2CO_3	3.0	150	DMSO	45
5	K_2CO_3	3.0	81	ACN	Trace
6	K_2CO_3	3.0	66	THF	Trace
7	K_2CO_3	3.0	140	DMF	81
8	K_2CO_3	2.0	140	DMF	81
9	K_2CO_3	1.0	140	DMF	Trace

Our results for the synthesis of pyrazolo[1,5-*a*]quinazolin-5(4*H*)-ones **15** from reaction of **4**, **5** with **14** are shown in Table 2.4. The initial acylation was performed in DMF using 2 equiv of K_2CO_3 at -10 ºC for 15 min. The reaction was then warmed to room temperature and stirred for an additional 15 min. The final ring closure was accomplished by heating this mixture at 140 ºC, in the same flask, for a period of 30–60 min. Work-up consisted of removing the solvent under vacuum, slurrying the crude product in water to remove the base, filtering the solid, and washing with methanol/ether (2:1). Some cases required chromatographic purification, and this was accomplished on a short silica gel column eluted with methanol/chloroform (1:9). Employing this standard protocol, yields were consistently between 75–93%, regardless of the level of aromatic activation.

Our yields for the preparation of pyrazolo[1,5-*a*]pyrido[3,2-*e*]pyrimidin-5(4*H*)-ones **16** from 2-chloronicotinoyl chloride (**7**) and **14** are shown in Table 2.5. These reactions are terminated by S_NAr addition to a 2-chloropyridine moiety, and although the leaving group was less reactive, the polarized C=N bond and secondary activation by the ortho amide carbonyl facilitated the final ring closure. Only the ester-substituted pyrazole **14e**[79] failed to give the heterocyclic product in good yield. In this case, the reaction produced an inseparable mixture of three products, which included the desired ester and the corresponding acid as the major components. In this reaction, the ester group underwent facile hydrolysis during workup of the fused pyrazolopyridopyrimidinone product, which required more basic conditions for isolation. Attempts to remove the acid by extraction, even with mild base, led to additional ester cleavage. Apart from this one setback, the yields (66–87%) were similar to those achieved with the above fluoroaromatic substrates and the experimental details were essentially the same.

Table 2.4. Summary of pyrazolo[1,5-*a*]quinazolin-5(4*H*)-ones **15**



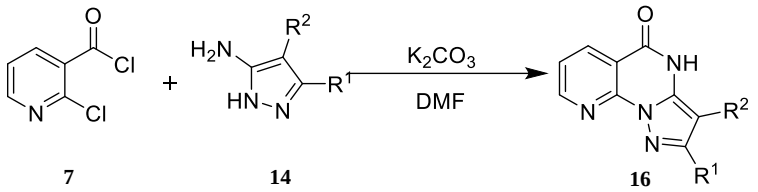
4 (X = NO_2)
5 (X = H)

14

15

Substrate	14	R^1	R^2	Product	% Yield
4	**a**	H	H	**15a**	82
	b	CH_3	H	**15b**	78
	c	*c*-C_3H_5	H	**15c**	76
	d	4-CH_3Ph	H	**15d**	78
	e	CO_2Et	H	**15e**	92
	f	H	CN	**15f**	88
	g	2-thienyl	H	**15g**	80
5	**a**	H	H	**15h**	81
	b	CH_3	H	**15i**	75
	c	*c*-C_3H_5	H	**15j**	79
	d	4-CH_3Ph	H	**15k**	77
	e	CO_2Et	H	**15l**	89
	f	H	CN	**15m**	93

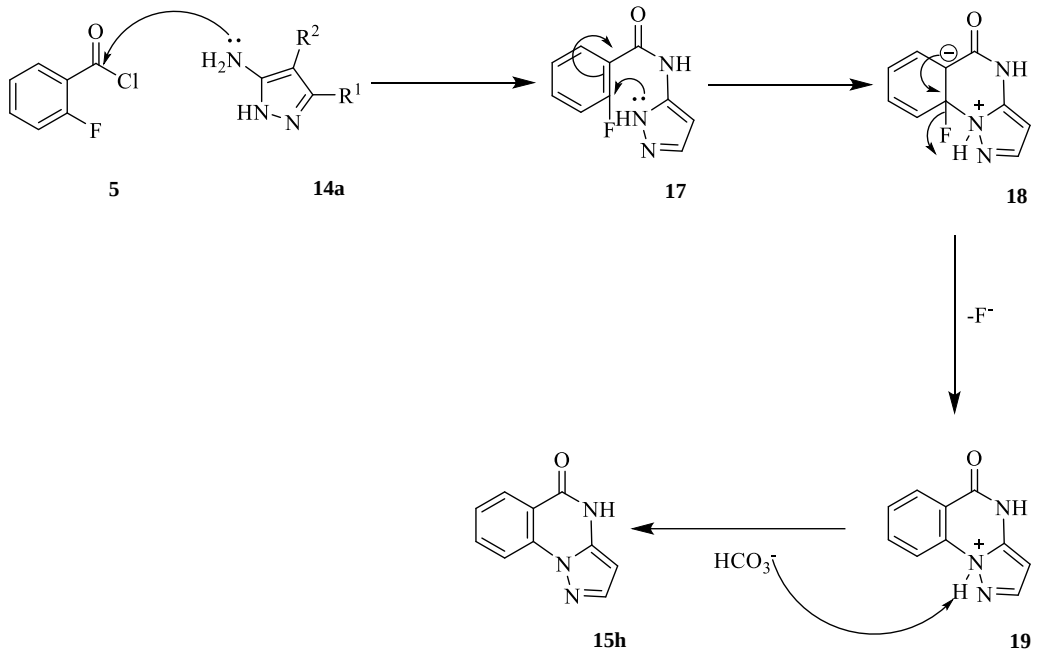
Table 2.5. Pyrazolo[1,5-*a*]pyrido[3,2-*e*]pyrimidin-5(4*H*)-ones 1**6** from **7** and **14**



7 **14** **16**

14	**R^1**	**R^2**	**Product**	**% Yield**
a	H	H	**16a**	66
b	CH_3	H	**16b**	71
c	*c*-C_3H_5	H	**16c**	78
d	4-CH_3Ph	H	**16d**	82
f	H	CN	**16f**	87

The presumed mechanism for the process is illustrated in Scheme 2.3 for the formation of **15h**. Initial amide formation by the reaction of acid chloride **5** with the 5-amino group of pyrazole **14a** at -10 ^oC gave amide **17**. This intermediate was isolated in the synthesis of **15h** confirming that acylation of the C5 amino group is the first step of the sequence. In the second stage of the process at 140 ^oC, N1 of the pyrazole would attack the fluorine-substituted carbon of the aromatic ring to give dipolar intermediate **18**. Rearomatization of **18** with loss of fluoride would then give **19**, and final deprotonation by the carbonate base would yield product **15h**. Interestingly, the same product was isolated in identical yield from the reaction of both 5-amino- and 3-amino-1*H*-pyrazole-4-carbonitrile with **5**. Theoretical and spectroscopic studies have shown that 3- and 5-substituted pyrazoles are in tautomeric equilibrium in polar aprotic media, and thus, there is ample precedent for equilibration of these two structures to give the same final product.[80-81]



Scheme 2.3. Presumed mechanism for **15h**

2.2.4 Conclusion

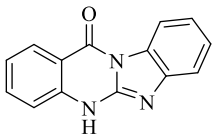
In conclusion, we have developed an efficient synthesis of pyrazolo[1,5-*a*]quinazolin-5(4*H*)-ones and pyrazolo[1,5-*a*]-pyrido[3,2-*e*]pyrimidin-5(4*H*)-ones using a sequential acylation–S_NAr reaction. The strategy involves reaction of the 1,3-disposed electrophilic sites in the 2-haloaroyl chlorides with the similarly disposed nucleophilic sites in the 5-amino-1*H*-pyrazole reactants to construct the central six-membered ring of the fused heterocyclic targets. The reaction is carried out in a single flask and the products are isolated with a minimum of purification effort.

2.2.5 Benzo[4,5]imidazo[2,1-*b*]quinazolin-12-ones and benzo[4,5]imidazo-[1,2-*a*]pyrido[2,3-*d*]pyrimidin-5-ones

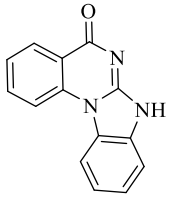
Benzimidazoles and quinazolinones are important structural units found in biologically active compounds. Numerous derivatives of these structures are found individually in drugs used to treat a wide variety of medical conditions.[82-85] Commercial benzimidazole-based drugs are used as antihelmintics, antiulceratives, and antihistimines. Quinazolinones also possess beneficial

pharmacological properties and are in use or under investigation as anticancer, antiviral, antimicrobial, antihypertensive, anti-inflammatory, and analgesic agents.

Fused-ring structures incorporating the benzimidazole and quinazolinone systems have also been prepared and investigated (Figure 2.2). An early report disclosed that benzo[4,5]imidazo[2,1-*b*]-quinazolin-12(5*H*)-one (**20**) exhibited potent immunosuppressive activity.[86] Additionally, derivatives of **20** as well as benzo[4,5]imidazo[1,2-*a*]quinazolin-5(7*H*)-one (**21**) are readily intercalated into DNA, and thus, may exhibit antiproliferative activity in human tumor cell lines.[86-88] Finally, in addition to their potential as anticancer agents, independent studies have also investigated these planar heteroaromatic systems as electron transport and emitter materials.[89]



20



21

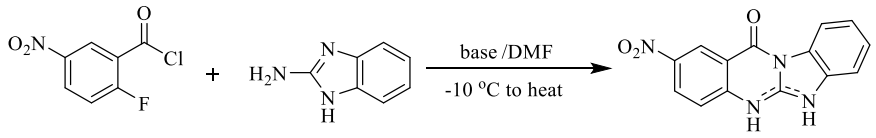
Figure 2.2. Benzo[4,5]imidazo[2,1-*b*]quinazolin-12(5*H*)-one (**1**) and benzo[4,5]imidazo[1,2-*a*]quinazolin-5(7*H*)-one (**2**) antitumor compounds.

To date, syntheses of polycyclic aromatic structures related to **20** have been reported using three different strategies. One approach employed an acylation–S_NAr sequence between 2-halo-[90] or 2-sulfo-[91] substituted benzimidazoles and anthranilic acid derivatives. A second synthesis involved the condensation of methyl 2-isothiocyanatobenzoate esters with *o*-phenylenediamine.[88] Two related reports outlined a third entry to these systems *via* a copper-catalyzed Ullman coupling of 2-bromobenzoic acid with 1-alkyl-2-aminobenzimidazoles[87] and a similarly promoted domino reaction between a 2-bromo-*N*-(2-halophenyl)benzamide with cyanamide.[92] Synthetic routes to compounds having the framework found in **21** have also been reported. Two articles documented a sequence involving acylation of 2-aminobenzimidazole with 2-haloaryloyl chlorides, followed in a separate step, by cyclization in boiling pyridine or diphenyl ether (20–78%).[93-94] Two

additional disclosures utilized a copper-mediated coupling reaction: one joined 2-aminobenzimidazole with 2-bromobenzoic acid in refluxing DMF (93%),[95] and the other promoted displacement of halogen from *N*-alkyl-2-halobenzamides by N1 of benzimidazole under anaerobic conditions in DMSO at 120 °C, and then, upon exposure to air at this same temperature, produced oxidative amidation at C2 of the benzimidazole to close the ring (54–98%).[96] The acylation–S_NAr approaches to **20** and **21** described relatively few examples, and thus, the reaction scope for these two methods was limited. Those catalyzed by copper, showed broader applicability, but likely yielded products containing metal impurities, which would require removal prior to use as a drug.

Our strategy was based on two earlier projects, namely synthesis of isoquinolin-1(2*H*)-ones[97] and pyrazoloquinazolinones[98] involving a one-pot acylation–S_NAr sequence that exploited the 1,3-disposed nucleophilic centers in 2-aminobenzimidazole with the similarly positioned electrophilic sites in a 2-haloaroyl chloride to generate the central six-membered ring. Interestingly, two regioisomeric products were possible from the current reaction, one derived from initial acylation of the amino substituent on the benzimidazole to give structures related to **21** and the other from acylation at the saturated benzimidazole nitrogen[93,99] to give regioisomers similar to **20**. We anticipated that treatment of 2-fluoro-5-nitrobenzoyl chloride (**4**) with 2-aminobenzimidazole (**22**) in the presence of base would proceed by a sequence involving acylation of the amino function of **22** followed by an S_NAr ring closure to give substituted derivatives of **21**. In practice, however, product **23a**, with the ring system found in **20**, was produced. Using *N*,*N*-dimethylformamide (DMF) as the solvent, **4** and **22** were mixed in the presence of different bases at -10 °C, and then heated. When complete, the reaction was worked up and purified to give the yields of **23a** shown in Table 2.6.

Table 2.6. Reaction optimization results for **23**



4 **22** **23a**

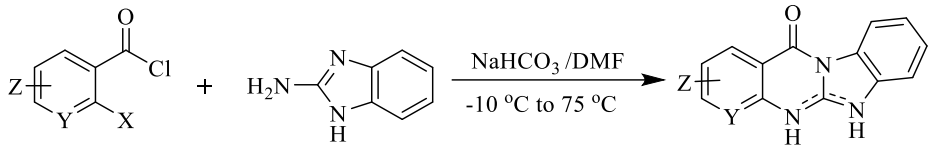
Entry	Base (2 equiv)	Temp (°C)	Time (h)	% Yield
1	TEA	140	12.0	15
2	Pyridine	140	12.0	18
3	DIPEA	140	12.0	26
4	K_2CO_3	140	0.5	88
5	Na_2CO_3	140	1.0	88
6	$KHCO_3$	140	1.0	88
7	$NaHCO_3$	140	1.0	88
8	**$NaHCO_3$**	**75**	**1.0**	**88**
9	$NaHCO_3$	60	5.0	53
10	$NaHCO_3$	45	5.0	38

Organic bases (TEA, pyridine, and DIPEA) in DMF at 140 °C failed to give acceptable conversions, but sodium carbonate and potassium carbonate, as well as the corresponding bicarbonates, promoted complete conversion at 140 °C within 1 h. Since sodium bicarbonate is mild as well as inexpensive, we sought to optimize the temperature using this base. Variation of this parameter revealed that the reaction proceeded at temperatures as low as 75 °C, but slowed dramatically at 45 °C and 60 °C. Thus, our optimized procedure involved treating 2-

aminobenzimidazole (1.2 equiv) with the acid chloride (1.0 equiv) in the presence of $NaHCO_3$ (2 equiv) in DMF at -10 ^oC for 30 min, followed by heating to 75 ^oC for 0.5–1 h.

Application of these conditions to substrates **4a-h** furnished high yields of the target heterocycles **23a-h**, allowing slightly broader reaction scope with respect to substitution on the acid chloride than our previous synthesis of pyrazoloquinazolinones. Most reactions proceeded at 75 ^oC, while 2,3,4,5,6-pentafluorobenzoyl chloride (**4d**) gave a near quantitative yield of **23d** after 1 h at 23 ^oC (Table 2.7). The reaction workup involved removal of DMF under vacuum, dilution with distilled water and filtration. The resulting solid was then stirred with ethanol at reflux, cooled and filtered. While the benzimidazoquinazolinone product did not dissolve significantly in hot ethanol, soluble impurities were removed by this treatment. The low solubility of the products in common organic solvents rendered chromatographic purification ineffective as a means of purification. Poor mass balances were obtained when this was attempted.

Table 2.7. Cyclizations to form products **23a-h**



4a-g and 5 (X, Y, Z – see below) **22** **23**

Substrate	X	Y	Z	Pdt	Z	% Yield[a]
4a	F	CH	5-NO_2	**23a**	2-NO_2	88
4b	F	CH	5-F	**23b**	2-F	86
4c	F	CH	6-F	**23c**	1-F	93
4d	F	CF	4,5,6-F	**23d**	1,2,3-F	96[b]
4e	F	CH	4-Me	**23e**	3-Me	76
4f	F	CH	4-Br	**23f**	3-Br	78
4g	Cl	N	H	**23g**	H	90
5	F	CH	H	**23h**	H	87

[a]Isolated yield
[b]Reaction was completed in 1 h at 23 °C

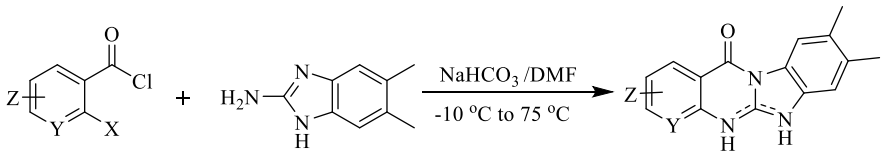
In order to broaden the scope of the reaction, we prepared 2-amino-5,6-dimethylbenzimidazole (**24**) from 4,5-dimethylbenzene-1,2-diamine and cyanogen bromide according to a literature procedure.[100] Reaction of **4a-g** and **5** with **24** using our standard protocol generated the corresponding 8,9-dimethylbenzimidazoquinazolinones **25a-h** in high yields (Table 2.8). Again, the perfluorinated acid chloride afforded excellent conversion to the acylation-S_NAr product at 23 °C.

Previous syntheses of N5- or N6-alkylated benzo[4.5]imidazo-[2,1-*b*]quinazolin-12-ones were reported with unambiguous characterization data,[96] though most of these papers did not report ^{13}C

NMR spectra. As the current compounds are not substituted at either of these sites, spectral interpretation proved considerably more difficult. While the ^{1}H NMR spectra were reasonably sharp, it was observed that many of the absorptions in the ^{13}C NMR spectra were broadened to a point where they could not be observed. It is interesting to note that benzimidazoles normally exist as tautomeric structures having partial double bond character between C2–N1 and C2–N3,[101-102] with H exchanged between the two nitrogens. We have observed broadened ^{13}C NMR signals resulting from this phenomenon, in a previous syntheses of these compounds.[103]

In the current systems, tautomerization involved a proton shift between N6 of the benzimidazole moiety and N5 exocyclic to the benzimidazole; due to its tertiary structure and electron-deficient substitution, N11 was not involved in this tautomerization. The NH proton was often not observed in the ^{1}H NMR, presumably due to H-bonding with the solvent, which would shift the signal well beyond the normal chemical shift range.[104] The broadened signals in the ^{13}C NMR spectra for the current products clearly indicated that the bonding situation in these materials was not straightforward. Earlier studies failed to report ^{13}C NMR spectra, which is understandable since our attempts to acquire these data were hampered by the tautomeric nature and low solubility of the compounds (even at 110 ^{o}C in DMSO-d_6). In particular, the aromatic carbons for most of the products as well as the methyl carbons of **25a-h** were broadened significantly, particularly for **23a**,**c,e** and for **25b**,**c**,**e**,**h**. Resolution of this problem was accomplished by treatment of these products with acetyl chloride and triethylamine, which selectively acylated N6 as illustrated below (Table 2.9). An X-ray structure of 6-acetyl-2-nitro-benzo[4,5]imidazo[2,1-*b*]quinazolin-12(6*H*)-one (**26a**), derived from **23a** (Figure 2.3), confirmed the site of reaction.

Table 2.8. Cyclizations to form products **25a-h**



4a-g and 5 **24** **25**

Substrate	X	Y	Z	Pdt	Z	% Yield[a]
4a	F	CH	5-NO_2	**25a**	2-NO_2	91
4b	F	CH	5-F	**25b**	2-F	87
4c	F	CH	6-F	**25c**	1-F	95
4d	F	CF	4,5,6-F	**25d**	1,2,3-F	98[b]
4e	F	CH	4-Me	**25e**	3-Me	80
4f	F	CH	4-Br	**25f**	3-Br	84
4g	Cl	N	H	**25g**	H	95
5	F	CH	H	**25h**	H	83

[a]Isolated Yield
[b]Reaction was completed in 1 h at 23 °C

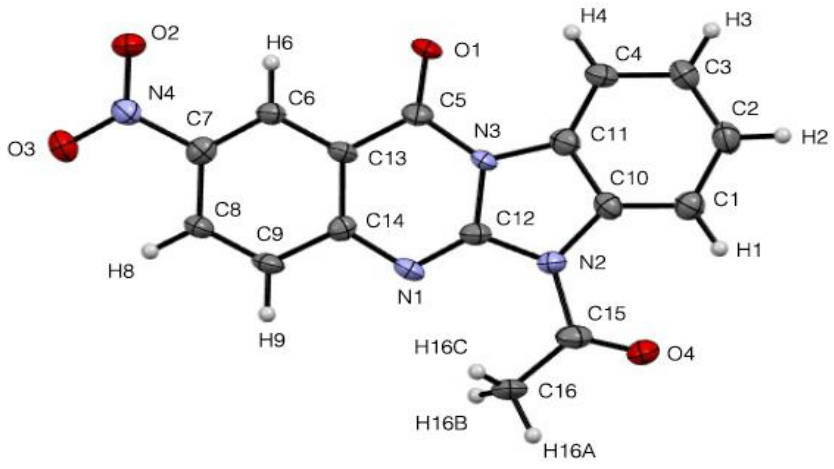
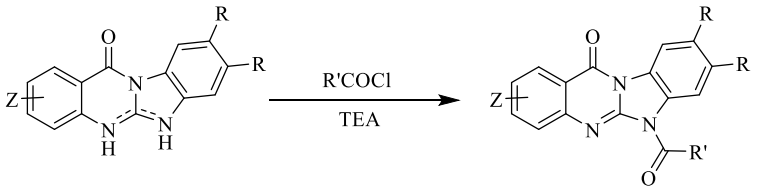


Figure 2.3. X-ray structure of **26a** (CCDC 1424687).

Most of the acylated derivatives showed improved solubility and gave sharp peaks in the ^{13}C NMR spectrum at 75 °C in DMSO-d_6. However, the acetamides of **25c** and **25f** also proved to be

highly insoluble, and thus, the hexanoyl derivatives were prepared. The hexanamides presented no solubility problems and the spectra were readily acquired in $CDCl_3$ at 23 °C. As an added benefit, these derivatization experiments revealed a facile method for modulating the solubility of these compounds. Interestingly, some structures did not show significant signal broadening in the ^{13}C NMR. This was noted in products derived from acid chlorides **4d** and **4g**, which incorporated electron deficient fused tetrafluorobenzo **25d** and pyrido **25g** moieties. These derivatives gave sharp signals in their ^{13}C NMR spectra. A possible explanation for this observation is that the electron-deficient ring draws the double bond away from the benzimidazole ring making tautomerization less important. Furthermore, positioning of the conjugated double bond in the six-membered ring exo to the five-membered imidazole ring should also be favorable. Other structures derived from acid chlorides bearing only one electron-withdrawing group (e.g. **4a**,**b**,**c**) were not sufficiently electron deficient to elicit this effect.

Table 2.9. Acylation of N6 to block tautomerization

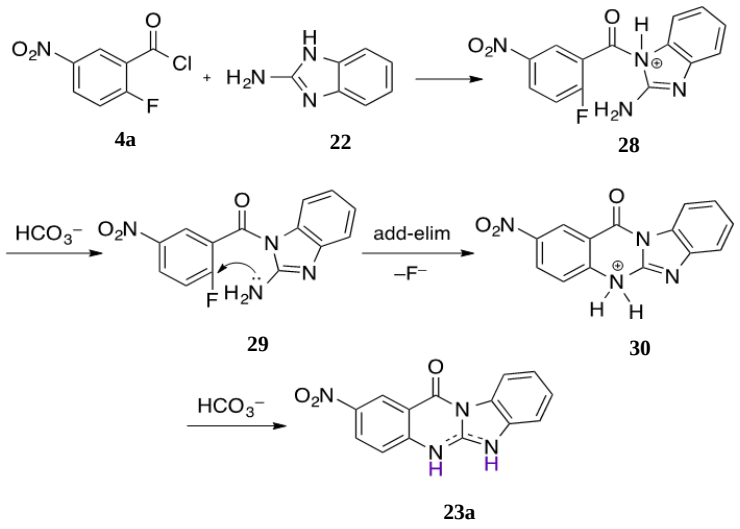


23 or 25 **26 or 27**

Substrate	R	R’	Z	Pdt	% Yield
23a	H	Me	2-NO_2	**26a**	94
23c	H	Me	2-F	**26c**	96
23e	H	Me	3-Me	**26e**	92
25b	Me	Hex	2-F	**27b**	85

25c	Me	Me	1-F	**27c**	93
25e	Me	Hex	3-Me	**27e**	97
25h	Me	Me	H	**27h**	88

The presumed mechanism to convert **4a** and **22** to **23a** is depicted in Scheme 2.4. Since bicarbonate is an insufficiently strong base to deprotonate 2-aminobenzimidazole (**22**, pKa *ca* 16),[105-106] it serves to scavenge protons after the various addition-elimination processes take place. Following acylation of **22** at N1 by **4a**, bicarbonate would deprotonate intermediate **28** to give amide **29**. At this stage, the amino nitrogen would attack the fluorinated carbon initiating an S_NAr addition-elimination to give **30**. Final deprotonation by the second equivalent of base would then afford benzimidazoquinazolinone **23a** as a mixture of tautomers.



Scheme 2.4. Presumed mechanism for the reaction of **4a** and **22** to give **23a**.

2.2.6 Conclusion

In conclusion, we have developed a one-pot sequential procedure to prepare benzo[4,5]imidazo[1,2-*a*]quinazolin-12-ones and benzo[4.5]imidazo[1,2-*a*]pyrido[2,3-

d]pyrimidin-5-ones using an acylation–S_NAr sequence. The strategy involves the reaction between the 1,3-disposed nucleophilic centers in 2-aminobenimidazole and the similarly arranged electrophilic sites in the 2-haloaroyl chlorides to construct the central six-membered ring of the fused heterocyclic targets. The products are formed in high yields by a procedure that eliminates high temperatures, strong bases, and metal catalysts. The ^{13}C NMR spectra of the products exhibit broad signals, which suggest that the structures are tautomeric across the N5–C5a–N6 triad. Acylation of these products results in exclusive reaction at N6. This locks the double bond into the six-membered ring and improves solubility, making NMR characterization more straightforward. A presumed mechanism is presented to account for the observed transformation.

2.2.7 1,3,4-Oxadiazole synthesis promoted by NH_4Cl

The 1,3,4-oxadiazole scaffold has attracted considerable attention in the field of medicinal chemistry as depicted in Figure 2.4.[107] Due to the broad commercial potential of 1,3,4-oxadiazoles, numerous methods for their synthesis have been developed over the years. Most approaches are either multi-step or involve the cyclization of hydrazides using harsh reagents such as phosphorus oxychloride, thionyl chloride, sulfuric acid, zirconium(IV) chloride, XtalFluor-E®, Burgess reagent, Deoxo-Fluor®, acid chlorides, Nafion® NR50, or acetic acid, under reflux or microwave heating.[108] Due to the caustic nature of these reagents, sensitive functional groups are often incompatible with these earlier methods. To address this problem, we have developed a mild protocol, which involves the formation of 1,3,4-oxadiazoles from arylhydrazides and orthoesters promoted by catalytic NH_4Cl.

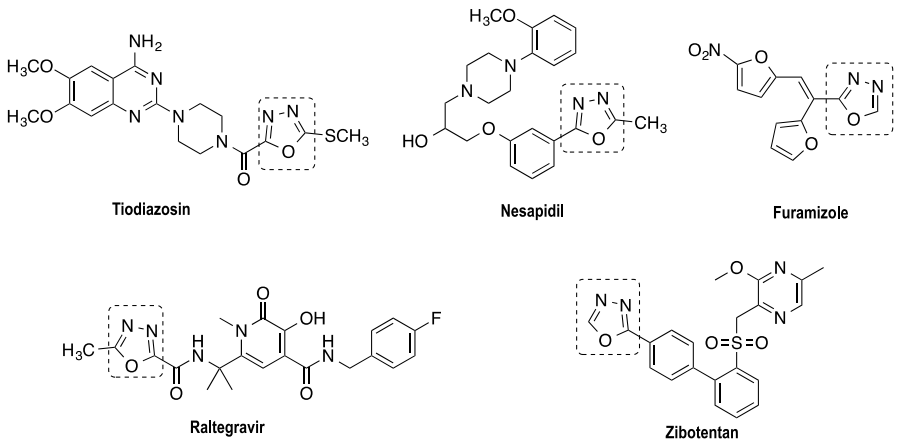
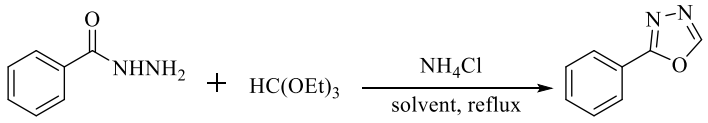


Figure 2.4. Drug containing a oxadiazole ring

In recent years, we have found that NH_4Cl is a highly efficient and mild catalyst for the synthesis of benzo-fused heterocycles such as benzimidazoles, benzoxazoles, and benzothiazoles,[103] and also for the preparation of α-aminonitriles using a variant of the Strecker synthesis.[109] To extend the scope of this catalyst, optimization studies were performed for the current reaction using benzhydrazide (1.0 equiv) and triethyl orthoformate (1.1 equiv). The optimized transformation occurred using 30 mol% of NH_4Cl in refluxing ethanol, which afforded a 96% yield of the corresponding oxadiazole in less than 1 h. Lower catalyst loadings gave slow and often incomplete reaction, while more catalyst gave no additional rate enhancement. The use of absolute EtOH proved essential to achieve maximum conversion for these reactions. Attempts to use other solvents (THF, dichloroethane, CH_3OH, dioxane, CH_3CN, benzene, 10:1 EtOH/H_2O or 1:1 EtOH/H_2O) either produced lower yields or required longer reaction times (Fig. 2.5). The current procedure represents a considerable improvement over a previously published uncatalyzed route that required 18 h and a five-fold excess of the orthoester.[110-111]



31 **39a** **40a**

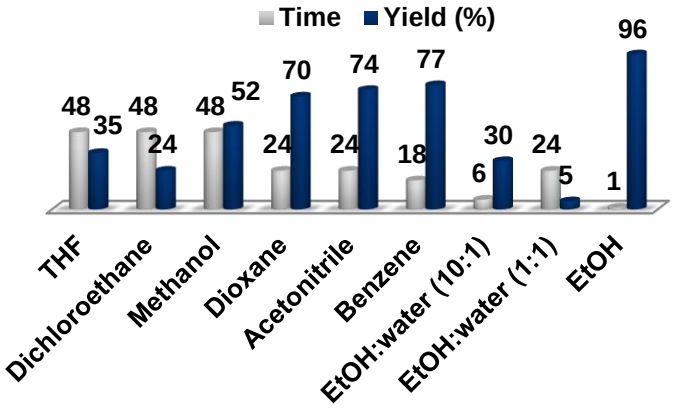
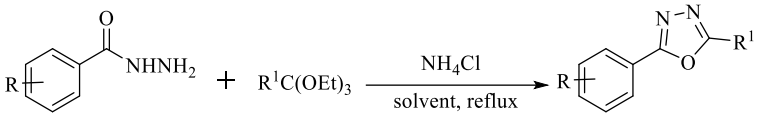


Figure 2.5. Effect of solvent with time in the reaction

The scope of this reaction was studied by refluxing a series of arylhydrazides with various triethyl orthoesters in EtOH using 30 mol% of NH_4Cl. Our results are summarized in Table 2.10. The mild reaction conditions offered a wide range of functional group tolerance on the arylhydrazide including methyl, methoxy, chloro, bromo, and nitro. In most cases, the yields were high, and the products were formed cleanly. Solid products were isolated directly from the reaction mixture and did not require further purification. Oils required purification by elution through a short column of silica gel. The reaction was successful with both electron-releasing and electron-withdrawing substituents on the arylhydrazide reactant.

Table 2.10. Summary of 2- and 2,5-disubstituted 1,3,4-oxadiazoles



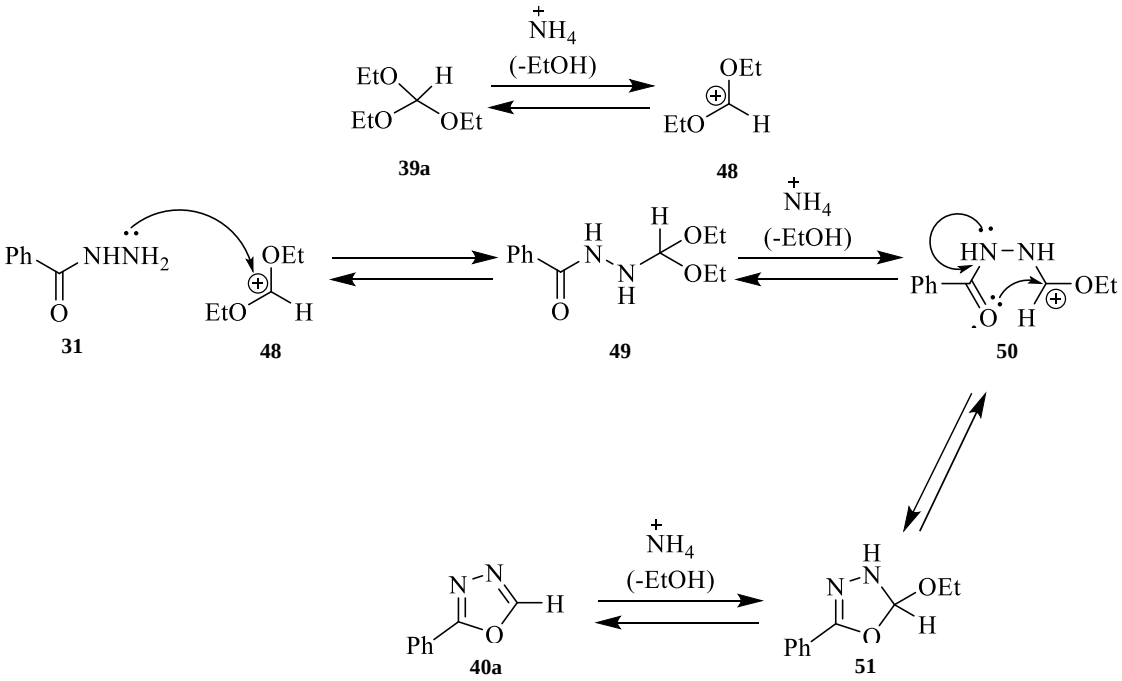
31-38 **39a-d** **40-47(a-d)**

31 (R = H); 32 (R = 4-CH_3)
33 (R = 4-OCH_3); 34 (R = 3-Br)
35 (R = 2-Cl); 36 (R = 4-Cl)
37 (R = 2-NO_2); 38 (R = 4-NO_2)

a (R^1 = H)
b (R^1 = CH_3)
c (R^1 = CH_2CH_3)
d (R^1 =Ph)

Entry	R	R^1	Yield	Entry	R	R^1	% Yield
40a	H	H	95	**43d**	3-Br	Ph	80
40b	H	CH_3	93	**44a**	2-Cl	H	28

40c	H	CH_2CH_3	98	**44d**	2-Cl	Ph	97
40d	H	Ph	96	**45a**	4-Cl	H	90
41a	4-CH_3	H	88	**45b**	4-Cl	CH_3	75
41b	4-CH_3	CH_3	53	**45c**	4-Cl	CH_2CH_3	95
41c	4-CH_3	CH_2CH_3	95	**45d**	4-Cl	Ph	70
41d	4-CH_3	Ph	96	**46a**	2-NO_2	H	22
42a	4-OCH_3	H	98	**46b**	2-NO_2	CH_3	25
42b	4-OCH_3	CH_3	90	**46c**	2-NO_2	CH_2CH_3	38
42c	4-OCH_3	CH_2CH_3	93	**46d**	2-NO_2	Ph	55
42d	4-OCH_3	Ph	97	**47a**	4-NO_2	H	74
43a	3-Br	H	82	**47b**	4-NO_2	CH_3	81
43b	3-Br	CH_3	89	**47c**	4-NO_2	CH_2CH_3	69
43c	3-Br	CH_2CH_3	86	**47d**	4-NO_2	Ph	92



Scheme 2.5. Proposed mechanism for the formation of 1,3,4-oxaidazole **40a**

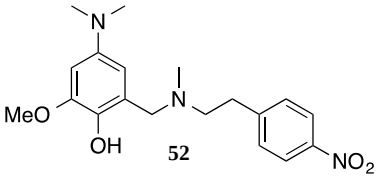
The yield of oxadiazole was only decreased when an electron-withdrawing group was positioned ortho to the hydrazide carbonyl. This presumably results from an electronic effect, which should exert a greater impact on the carbonyl reactivity from this position. Most notably, the presence of an electron-withdrawing chloro or nitro at the ortho position of the arylhydrazide resulted in lower yields, especially with non-aromatic orthoesters. A proposed mechanism for oxadiazole formation is given in Scheme 2.5. Initial protonation and loss of EtOH from **39a** would give the ether-stabilized carbocation **48**. Attack on this species by hydrazide **31** to give **49** would be followed by proton exchange and loss of a second molecule of EtOH to give **50**. Ring closure to generate **51** and elimination of EtOH would then afford oxadiazole **40a**.

2.2.8 Conclusion

In summary, we have developed an efficient and inexpensive approach to the synthesis of 2-substituted and 2,5-disubstituted 1,3,4-oxadiazoles using NH_4Cl as catalyst. The conditions are mild, and thus, compatible with a variety of functional groups. The optimized reaction is performed using 30 mol % of NH_4Cl in 100% EtOH and is generally complete within 1 h for orthoformate, orthoacetate, or orthopropionate, and 2–10 h for orthobenzoate. In most cases, the yields are high, and the isolated products require substrate and proceeds smoothly for both non-aromatic and aromatic orthoesters. Compared with earlier reports, the current reactions proceed in shorter time and require considerably less orthoester.

2.2.9 Nucleophilic addition across polarized vinyl arenes

The formation of a carbon-nitrogen bond by amine addition across a carbon-carbon double bond has been a promising atom efficient method since the early 1990's.[112-115] To our knowledge, most of the prevailing methods for hydroamination utilized transition metals as a catalyst. Rarely observed "anti-Markonikov" selectivity has been reported with Rh, Ru, Ti and Cu systems.[116-121] Likewise, no reports are available for the anti-



52

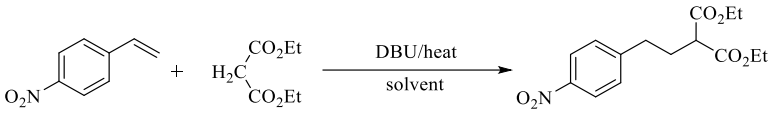
Figure 2.6. Structure of CDC25 phosphatases

Markonikov addition to vinyl styrene except the work reported by Dale *et al*.,[122] in 1954, who performed the reactionon electron-deficient systems using sodium methoxide in alcohol. This method however, is not optimum as it gives low yields and dimerization of the desired product. Apart from the necessity to develop better methods for the anti-Markonikov hydroamination of electron deficient vinylarenes, the resultant product can be used as a building block to prepare CDC25 phosphatases inhibitors such as **52** for cancer treatment.[123]

In this project we focused on developing an efficient route for hydroamination and nucleophilic addition across electron deficient vinyl arenes under metal free condition. Nucleophiles, such as enolates and amines, do not normally react with styrene double bonds. However, when an electron withdrawing substituent on the aromatic ring is conjugated with the double bond (at C2 or C4), the vinyl double bond assumes electrophilic character. We took advantage of this phenomenon and initially tried to perform additions across polarized vinylarenes using enolates generated by reaction of malonate esters with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU). This reaction proceeded smoothly, and thus, we sought to optimize the reaction conditions.

After optimizing the base stoichiometry, we sought to find a better solvent, and of all the solvents we tried (Table 2.11), acetonitrile provided the best result. Reactions in DMF and DMSO proceeded faster, but gave problems during product isolation. We also explored other bases besides DBU, including tetramethylguanidine, 4-(dimethylamino)pyridine (DMAP), imidazole, diazabicyclo[2.2.2]octane (DABCO), sodium hydride (NaH) and potassium *tert*-butoxide (*t*-BuOK). These experiments confirmed that DBU was the base of choice for this transformation (Table 2.12). Finally, we optimized the stoichiometry of the nucleophile. By reducing the amount of nucleophile to 1.5 equivalents, the reaction continued to provide good yields; however, less than this stochiometry resulted in a dramatic reduction in yield. The optimized conditions required the use of 1.5 equivalent of the nucleophile, 1 equivalent of base, and 1 equivalent of the vinylarene.

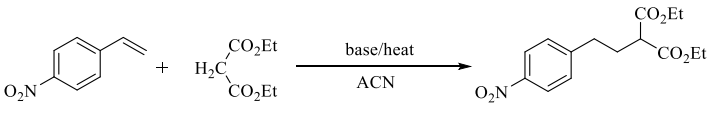
Table 2.11. Solvent optimization for addition to polarized vinylarenes



53a **54a** **55a**

Entry	Solvent	Time (h)	Yield (%)
1	DMF	2.0	56
2	Acetonitrile	4.0	93
3	DMSO	2.0	48
4	Ethanol	18	25
5	THF	10	62

Table 2.12. Optimization of base for addition to polarized vinyl arenes



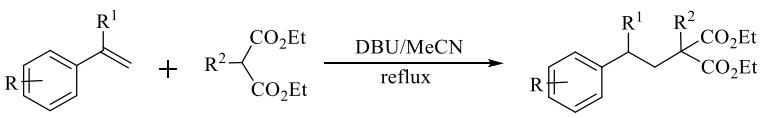
53a **54a** **55a**

Entry	Base	Equiv	Yield (%)
1	TMG	1.0	36
2	DMAP	1.0	28
3	Imidazole	1.0	45
4	DBU	1.0	93
5	DABCO	1.0	80
6	NaH	1.0	65
7	*t*-BuOK	1.0	23
8	DBU	0.2	26
9	DBU	0.5	59

10	DBU	0.7	75

With the optimized parameters in hand, we attempted to explore the scope of the reaction with various nucleophiles and substrates. The optimized conditions worked well for 4-nitrostyrene with various active methylene compounds like diethyl malonate (**54a**), diethyl methylmalonate (**54b**), and ethyl 2-oxocyclopentanecarboxylate (**56**), giving excellent yields of the products in 4-6 h. Active methylene compounds (Table 2.13) also added to 2-nitrostyrene, but yields were slightly lower, presumably due to steric hindrance created by the *ortho*-nitro group.

Table 2.13. Reaction using malonate donars



53
acceptor
1 equiv

54
donor
1.5 equiv

55

Acceptor	**Donor**	**Product**	**Yield (%)**

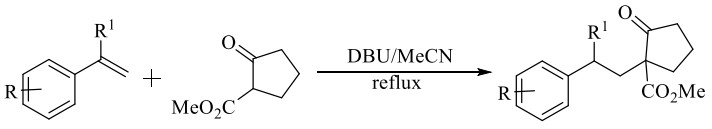
53a (R = 4-NO_2, R^1 = H)	**54a** (R^2 = H)	**55a** (R = 4-NO_2, R^1, R^2 = H)	97
53a (R = 4-NO_2, R^1 = H)	**54b** (R^2 = Me)	**55b** (R = 4-NO_2, R^1, R^2 = H)	93
53b (R = 4-NO_2, R^1 = Me)	**54a** (R^2 = H)	**55c** (R = 4-NO_2, R^1 = H, R^2 = Me)	87
53b (R = 4-NO_2, R^1 = Me)	**54b** (R^2 = Me)	**55d** (R = 4-NO_2, R^1, R^2 = Me)	85
53c (R = 2-NO_2, R^1 = H)	**54a** (R^2 = H)	**55e** (R = 2-NO_2, R^1, R^2 = H)	94
53c (R = 2-NO_2, R^1 = H)	**54b** (R^2 = Me)	**55f** (R = 2-NO_2, R^1 = H, R^2 = Me)	74
53e (R = 4-CN, R^1 = H)	**54a** (R^2 = H)	**55g** (R = 4-CN, R^1, R^2 = H)	58
53e (R = 4-CN, R^1 = H)	**54b** (R^2 = Me)	**55h** (4-CN, R^1 = H, R^2 = Me)	53

Modification of the vinylarene substrates to include 4-cyano- and 4-ethoxycarbonyl-substituted aromatic rings (Table 2.13) met with only limited success. A major problem with these activating groups was that they tended to competitively react with the nucleophiles under the conditions of the reaction. In the case of cyano-substituted acceptors, malonate nucleophiles added cleanly, but amine nucleophiles failed due to facile polymerization of the substrate. For the ethoxycarbonyl-derived arenes, it was not possible to isolate acceptable yields of addition products from any of the nucleophiles due to attack at the aromatic ester. Substitution on the vinyl group was also explored, and as expected, steric factors were found to be important in the reaction. Introduction of a methyl group α to the arene (α-vinyl carbon) of the 4-nitrostyrene had little effect on the efficiency of addition, while addition of methyl at the site of attack (β-vinyl carbon) in this same substrate allowed addition by only simple unsubstituted malonate.

These conditions were further extended for use in the addition of a cyclic β-ketoester (Table 2.14) such as methyl 2-oxocyclopentanecarboxylate (**56**). This relatively hindered substrate proceeded to react with 1-nitro-4-vinylbenzene (**53a**, 81%), 1-nitro-4-(prop-1-en-2-yl)benzene (**53b**, 82%) and 1-nitro-2-vinylbenzene (**53c**, 80%). In the reaction with **53b**, separation of the final mixture

yielded two diastereomeric products **57b** in nearly a 1:1 ratio. Separation by preparative TLC gave two products: isomer 1 (39%), an oil, and isomer 2 (43%), a white solid. A crystal of isomer 2 was obtained for X-ray analysis by slow diffusion of pentane into an ether solution of the two diastereomers. Solution of the structure showed that the isomer 2 was racemic methyl (*R,R)*-2-oxo-1-(2-(4-nitrophenyl)propyl)cyclopentanecarboxylate [(±)-*R,R*-**57b**] (Figure2.7) allowing assignment of isomer 1 as the racemic (±)-*R,S*-**57b**. *Note*: The unit cell for isomer 2 of **57b** contains one molecule of the *R,R* (top) and one molecule of the *S,S* diastereomer (bottom).

Table 2.14. Reaction using a cyclic β-keto ester



53
acceptor
1 equiv

56
donar
1.5 equiv

57

Acceptor	Product	Yield (%)
53a (R = 4-NO_2, R^1 = H)	**57a** (R = 4-NO_2, R^1 = H)	81

53b ($R = 4\text{-}NO_2$, R^1 = Me)	**57b** ($R = 4\text{-}NO_2$, R^1 = Me)	82
53c ($R = 2\text{-}NO_2$, R^1 = H)	**57c** ($R = 2\text{-}NO_2$, R^1 = H)	80
53d ($R = 2\text{-}NO_2$, R^1 = Me)	**57d** ($R = 2\text{-}NO_2$, R^1 = Me)	0
53e ($R = 4\text{-}CN$, R^1 = H)	**57e** ($R = 4\text{-}CN$, R^1 = H)	51

We further explored the feasibility of hydroamination of these polarized alkenes with morpholine (**58**), piperidine (**59**) and benzylamine (**60**) to give **61**-**63**. These additions also proceeded in high yield, but required longer reaction times than the enolate additions (12-18 h). Control experiments, with and without base, established that DBU was also required for good conversion in these reactions. For each of the amines, reaction only occurred with the 2- and 4-nitrophenyl-substituted substrates **53a-c** (see Table 2.15), as the robust conditions promoted rapid polymerization of the cyanophenyl derivative and degradation of the ester in the ethoxycarbonyl substrate. Yields were in the 78-95% range. Attempted addition to the 2- and 4-nitrostyrenes bearing a methyl group at the α-carbon gave excellent yields of the addition products (77-84%), while substitution at the β-carbon failed to proceed due to steric hindrance at the site of attack.

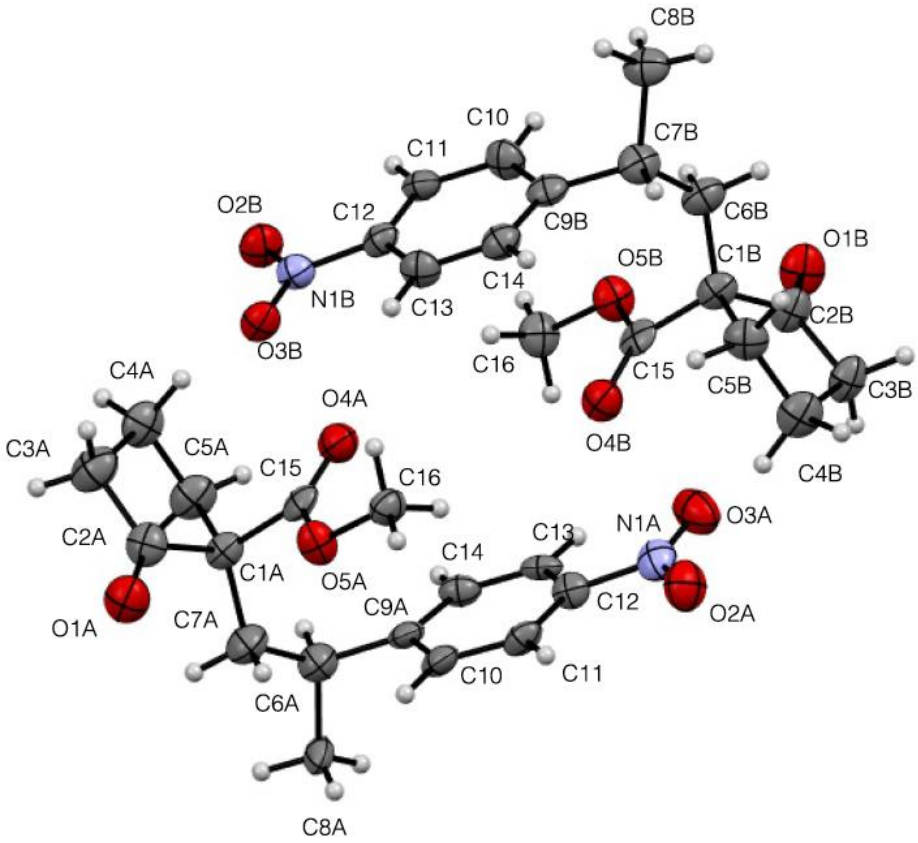
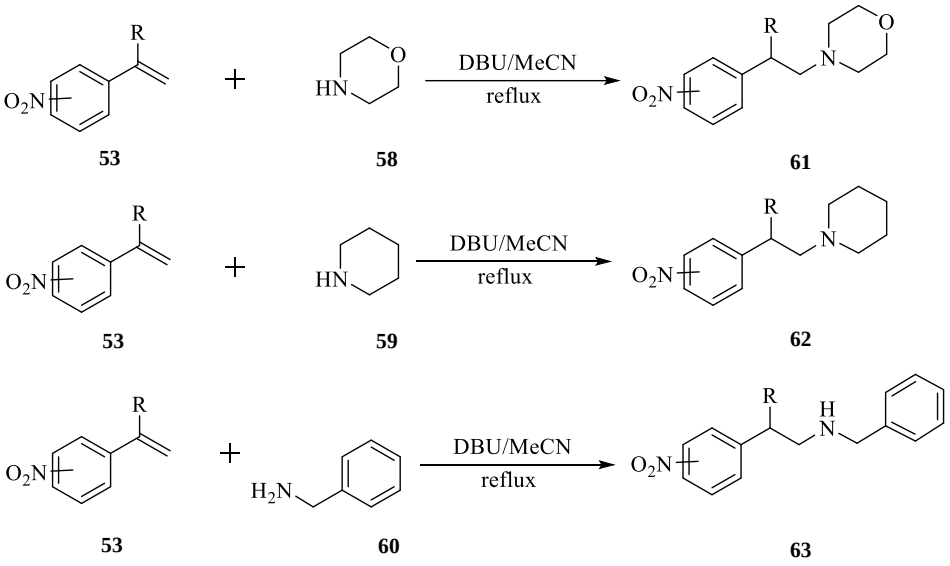


Figure 2.7. X-ray structure of (±)-*R*,*R*-**57b**

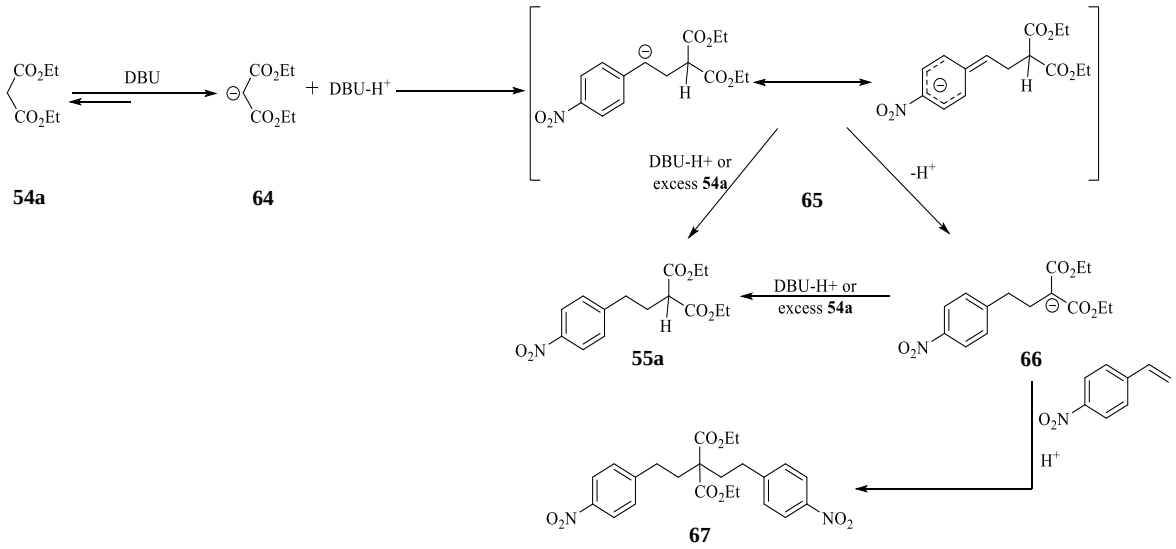
Table 2.15. Reaction with amine donors



Acceptor	Donor	Product	Yield (%)
53a (4-NO_2, R = H)	**58**	**61a** (4-NO_2, R = H)	95
53a (4-NO_2, R = H)	**59**	**62a** (4-NO_2, R = H)	93
53a (4-NO_2, R = H)	**60**	**63a** (4-NO_2, R = H)	82
53b (4-NO_2, R = Me)	**58**	**61b** (4-NO_2, R = Me)	86
53b (4-NO_2, R = Me)	**59**	**62b** (4-NO_2, R = Me)	84
53b (4-NO_2, R = Me)	**60**	**63b** (4-NO_2, R = Me)	77
53c (2-NO_2, R = H)	**58**	**61c** (2-NO_2, R = H)	85
53c (2-NO_2, R = H)	**59**	**62c** (2-NO_2, R = H)	88
53c (2-NO_2, R = H)	**60**	**63c** (2-NO_2, R = H)	78

The presumed mechanism for the reaction of **53a** with **54a** to give **55a** is depicted in Scheme 2.6. Deprotonation of **54a** using DBU would generate DBU-H^+ and carbanion **64**. In the presence of **53a**, **64** would add to the side chain double bond to generate adduct **65**. Intermediate **65** is stabilized in much the same manner as a Meisenheimer complex, but does not have a leaving

group at the site of attack, which would allow regeneration of the side chain double bond. Abstraction of the proton from DBU-H^+ (or excess **53a**) by **65** would then deliver the required single addition product **55a**. When the current reaction was performed using 0.2 equiv of DBU in DMF at 60 ^oC, a very poor yield of **55a** was obtained and more of the double addition product **67** was isolated. A likely explanation for this observation is that intramolecular proton transfer from the active methylene site to the benzylic anion in **65** is faster than intermolecular proton abstraction from the dilute DBU-H^+. This would generate **66**, which would then add a second molecule of **53a** and protonate to form **67**. Experiments to optimize the stoichiometry of DBU indicated that a full equivalent of this base relative to the vinylarene gave the highest conversion to the monoadduct. Although intramolecular proton transfer should still be faster, the presence of higher concentrations of DBU-H^+ along with excess **53a**, would make more protons available from intermolecular sources to stop the reaction at the single addition stage. Of course, the intramolecular proton transfer and double addition would not be an issue for reactions involving alkylated malonates such as **54b**.



Scheme 2.6. Presumed mechanism for additions to electron-deficient vinylarenes.

2.2.10 Conclusion

In conclusion, nucleophilic additions of enolates and amines to electron deficient vinylarenes substituted in the ortho or para positions by nitro, cyano, and ethoxycarbonyl have been explored and optimized. This reaction proceeded cleanly for nitro compounds **53a** and **53d** with malonates **54a** and **54b**, giving better yields than earlier reports without the need for added metal catalysts. The reaction is operationally simple and proceeds to give high yields in refluxing MeCN with DBU base after 4–6 h. Additions of the hindered β-ketoester **56** were also successful. For cyano compound **53e**, only the malonate and ketoester nucleophiles afforded the desired adducts, albeit in lower yields than those observed for the nitro compounds. Addition to the nitrostyrene substrate **54b** with a methyl group at the side chain position was also successful, but substrate **54c** with a β methyl group was too hindered for additions beyond unsubstituted malonate. The hydroamination procedure permitted the addition of primary and secondary amines **61**–**63** to nitrostyrenes **54a**, **54b**, and **54d** without added catalysts in MeCN at reflux for 12–18 h. Other acceptor incorporating 4-cyano underwent polymerization or degradation upon attempted addition of amines. The targets generated have high potential values for the synthesis of building blocks to assemble the backbone of several families of drug candidates.

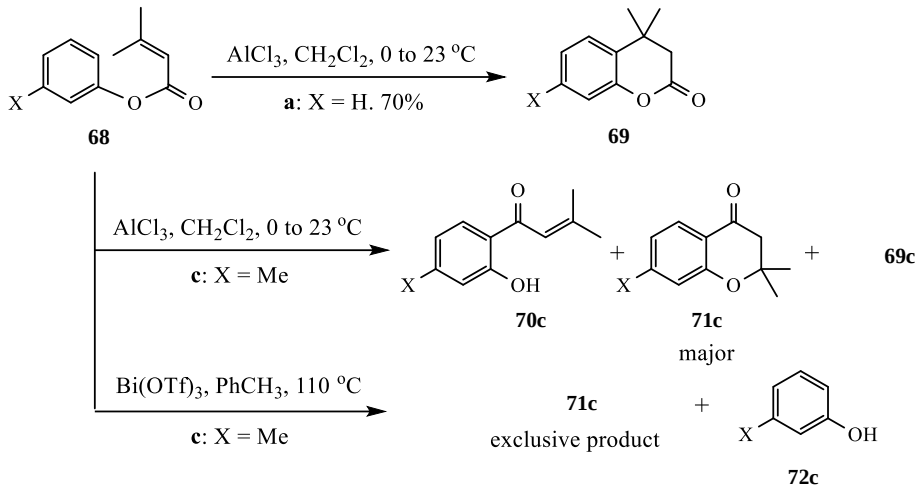
2.2.11 Bismuth triflate catalyzed synthesis of 4-chromanones

Efficient methods to produce oxygen heterocycles for use as building blocks in natural product and drug synthesis is a worthy endeavor. Among the heterocyclic scaffolds containing oxygen, 4-chromanones are widely dispersed in nature and constitute valuable substrates for drug synthesis.[124-125] For example, 4-chromanones are core structures in the synthesis of anti-estrogenic compounds used to treat breast cancer.[126] Various derivatives of this system are also inhibitors of SIRT2, an enzyme involved in age-related neurodegenerative disorders.[127] Finally, 4-chromanones have been used in the synthesis of somatostatin analogues which are currently under investigation for the treatment of osteoporosis[128] as well as certain stomach tumors.[129]

Previous methods for the synthesis of 4-chromanones have utilized a wide range of reaction protocols. One of the first generated 7-hydroxy-2,2-dimethyl-4-chromanone from highly activated resorcinol with 3,3-dimethylacrylic acid in the presence of $SbCl_3$.[130] Others have involved amine catalyzed condensation of *o*-hydroxyacetophenones with aliphatic ketones and aldehydes.[126-129, 131-133] Further reports have described the use of stoichiometric mercury(II) on aryl propargyl ethers,[134] addition of cuprates to chromones,[135] phosphorus oxychloride/zinc chloride with phenols and 3,3-dimethylacrylic acid,[136-137] the reaction of carboxylic acids with *o*-(trimethylsilyl)aryl triflates promoted by cesium fluoride[138] and a one-pot photo-Fries–oxa-Michael reaction.[139] Our approach involves the reaction of phenols bearing additional activating groups with 3,3-dimethylacrylic acid or crotonic acid to give a variety of tetra- and trisubstituted 4-chromanones, respectively. We achieved this, using bismuth(III) triflate to catalyze the one-pot conversion by a tandem esterification–Fries rearrangement–oxa-Michael sequence.

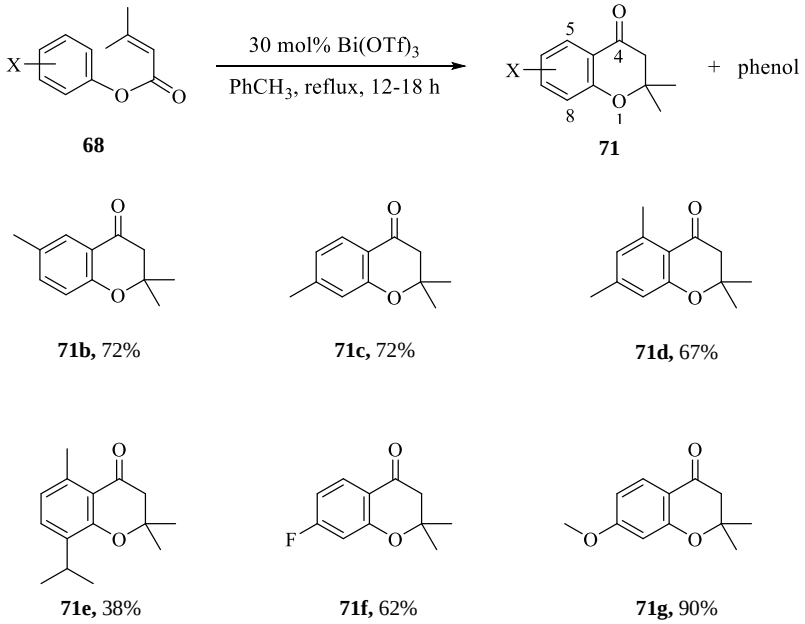
This project originated from our synthetic efforts to convert the phenyl ester of 3,3-dimethylacrylic acid **68a** to 2-chromanone **69a** (X = H). Cyclization of the simple phenyl ester is reported to give **69a** in >70% yield using 1.7 equiv of aluminum chloride,[140] and we have successfully used this procedure to access drug precursors of interest to our group. However, attempts to perform this reaction with esters of more activated aryl groups such as **68c** (X = Me) led to the formation of the Fries rearrangement product 1-(2-hydroxy-4-methylphenyl)-3-methyl-2-buten-1-one (**70c**, 18%) and significant quantities of 4-chromanone **71c** (65%) in addition to small amount of 2-chromanone **69c** (2%) (see Scheme 2.7). The 4-chromanone product likely arises *via* a Lewis acid promoted oxa-Michael reaction following the Fries rearrangement. While this may appear to be a reasonable synthesis of 4-chromanones, this reaction with aluminum chloride invariably led to mixtures of **69**, **70** and **71**. Thus, we sought a more selective route to 4-chromanone derivatives. Our research group had previously described the use of bismuth(III) triflate as a catalyst for Friedel-Crafts cyclizations of tertiary alcohols to produce chromans as

well as a variety of other heterocycles.[141] Attempting to use the similar strategy with ester **68c** revealed that the reaction of activated aryl



Scheme 2.7. Friedel-Crafts reaction of aryl ester of 3,3-dimethylacrylic acid

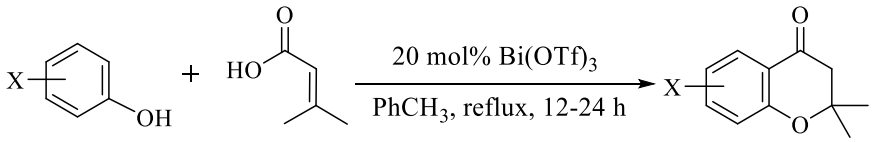
esters with bismuth(III) triflate afforded >70% of **71c** as the exclusive cyclized product, along with *ca.* 10% of the phenol from acid catalyzed cleavage of the ester. Additional examples showed that this process appeared to be broadly applicable to many substrates (see Scheme 2.8).



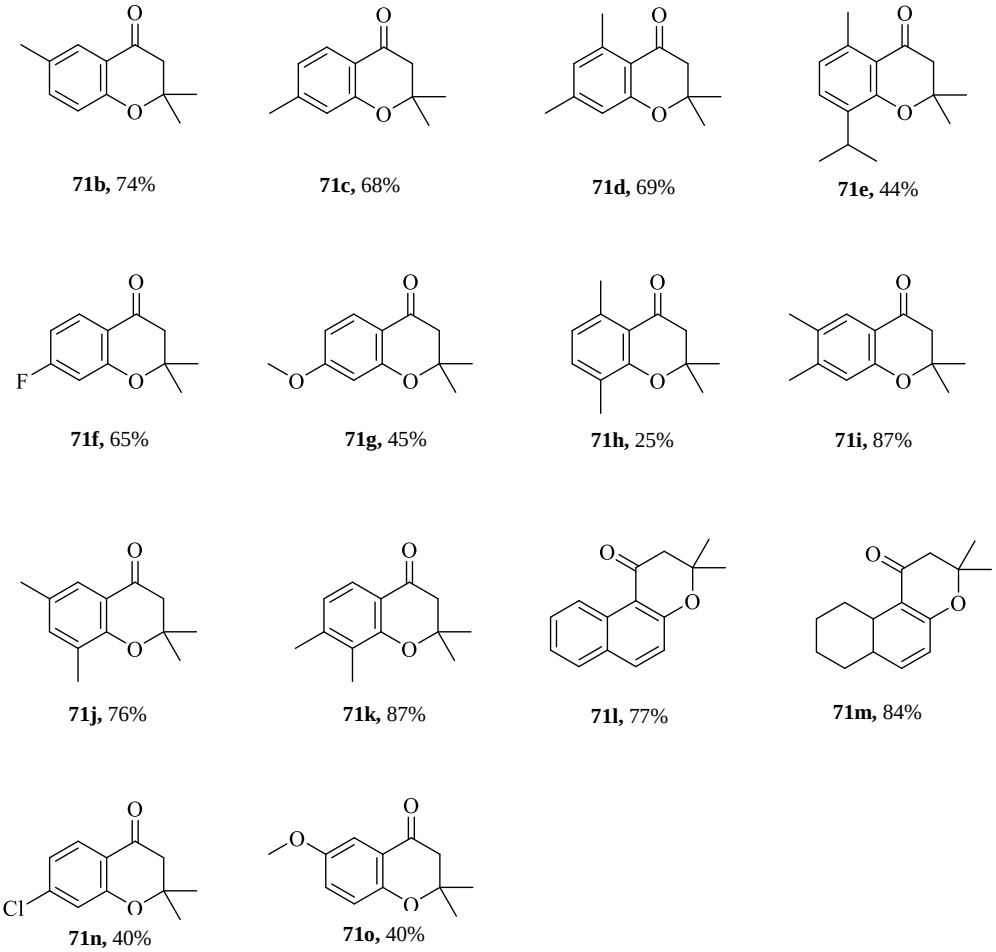
Scheme 2.8 4-Chromanones from aryl esters of 3,3-dimethylacrylic acid

In an effort to avoid the extra step of preparing the ester from the relatively expensive 3,3-dimethylacryloyl chloride, we sought to prepare the 4-chromanones directly from the phenol and 3,3-dimethylacrylic acid using bismuth(III) triflate. Fortunately, this route proved viable and gave fair to excellent yields of 4-chromanones with none of the 2-chromanone products. Among the substrates studied, phenol and 2-methylphenol were the lone disappointments, giving complex mixtures of products from which the 4-chromanones could not be isolated in pure form.

We were also successful in expanding this process to cyclizations with crotonic acid. However, attempts to further expand this reaction for ring closures of *trans*-cinnamic acid gave intractable mixtures with poor yields of the desired products. The results of our study of cyclizations using 3,3-dimethylacrylic acid and crotonic acid are shown in Schemes 2.9 and 2.10, respectively.



72 **71**



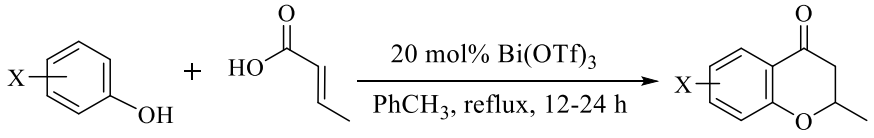
71b, 74% **71c,** 68% **71d,** 69% **71e,** 44%

71f, 65% **71g,** 45% **71h,** 25% **71i,** 87%

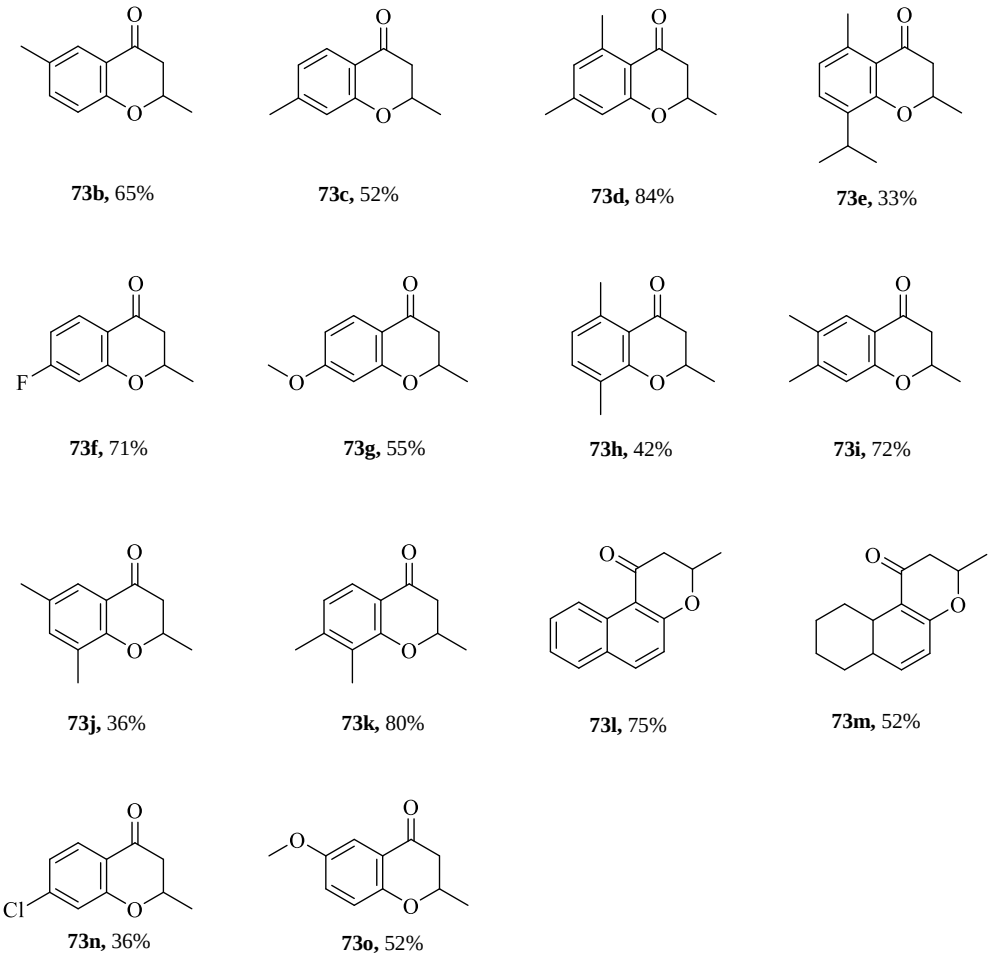
71j, 76% **71k,** 87% **71l,** 77% **71m,** 84%

71n, 40% **71o,** 40%

Scheme 2.9. 4-Chromanones from 3,3-dimethylacrylic acid



72 **73**



73b, 65% **73c,** 52% **73d,** 84% **73e,** 33%

73f, 71% **73g,** 55% **73h,** 42% **73i,** 72%

73j, 36% **73k,** 80% **73l,** 75% **73m,** 52%

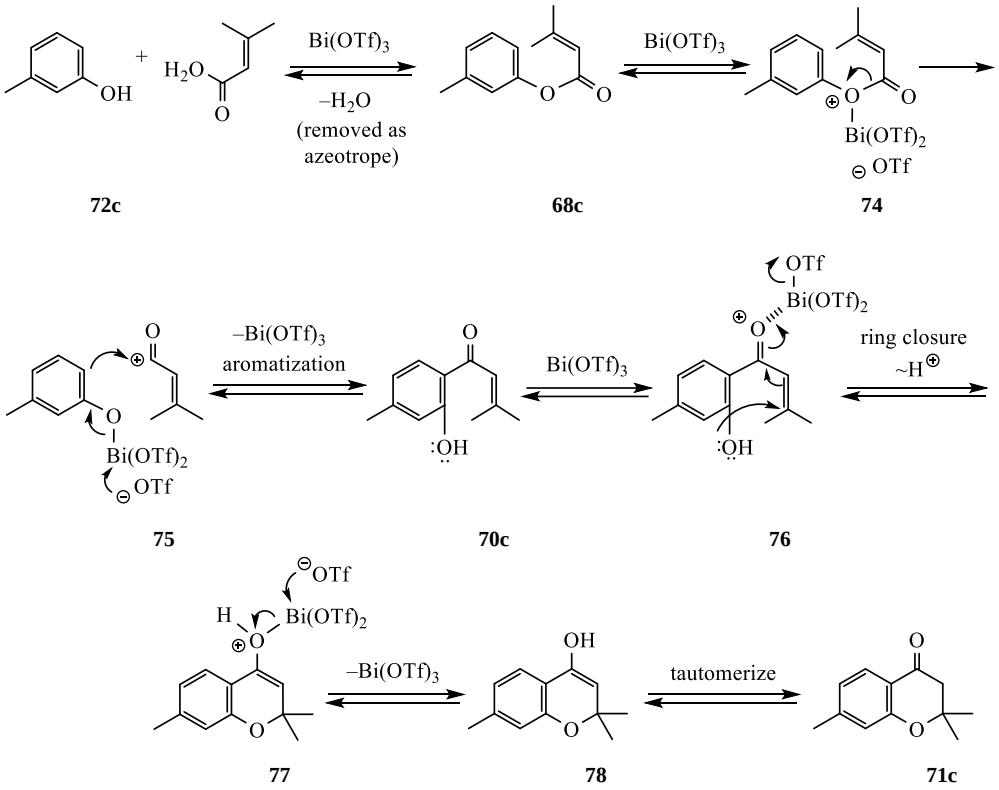
73n, 36% **73o,** 52%

Scheme 2.10. 4-Chromanones from *trans*-crotonic acid

Each reaction was run in toluene at reflux using a 1:1 ratio of phenol to carboxylic acid and 30 mol% of bismuth(III) triflate. The mixtures were refluxed for 12-18 h and monitored by TLC. When maximum conversions were attained, the reactions were cooled, concentrated under vacuum and the crude product, diluted with a small amount of chloroform, was applied to preparative thin layer chromatography (PTLC) plates. Elution 3-4 times with 5% ether in hexane (8-10% ether in hexane was used for the methoxy-substituted products) yielded 2-3 bands. In each case, the bright fluorescent blue band was the 4-chromanone, while others contained unreacted phenol or the aryl ester of the acid.

The reaction proceeded in moderate to high yields for a broad range of substrates, and the product was easily purified by chromatography. Good yields were achieved with nearly all of the methyl-substituted derivatives, and in 3-substituted phenols where the two ortho carbons were unsubstituted, closure occurred toward the less hindered position. Only 2-methylphenol failed to undergo clean reaction, and this could derive from steric hindrance at the hydroxyl group as well as the fact that the single methyl substituent would exert only a minimal activating effect at the aromatic carbon that will attack the acylium electrophile during the Fries rearrangement. Lower yields were also observed with 2,5-disubstituted phenols (entries **e** and **f**), which were sterically hindered and also tended to sublime into the condenser. Additionally, lower yields were observed with 3-chlorophenol (entry **m**), demonstrating the effect of the deactivating substituent.

The fluoro-substituted phenol (entry **l**) was unique in having an electron-withdrawing group while still giving a good yield of product. This is typical of fluorine-substituted aromatics which show high reactivity in the para position relative to the fluorine.[142-143] In 3-fluorophenol, the fluorine is para to the position that accepts the acylium ion during the Fries rearrangement, and thus, the conversion was better than expected. Interestingly, 2-naphthol (entry **j**) and 5,6,7,8-tetrahydro-2-naphthol (entry **k**) gave different regioselectivities in the ring closing reaction, with 2-naphthol closing at C1 (toward the fused ring) to generate an angular structure, while the tetrahydro derivative closed at C3 (away from the fused ring) to form the linear ring structure. Finally, the yields of 4-chromanones were slightly lower for reactions involving crotonic acid, as might be expected for a substrate with less stabilization of the acylium ion intermediate.



Scheme 2.11. A plausible mechanism for the $Bi(OTf)_3$ catalyzed synthesis of 4-chromanones

A brief outline of the presumed mechanism is shown for the conversion of **72c** to **71c** in Scheme 2.11. Close monitoring of the reaction by thin layer chromatography indicated that the first intermediate in the process is the aryl ester **68c**. While this process produces an equivalent of water, which could decompose the catalyst, the boiling toluene solvent serves to remove this by-product from the reaction by azeotropic distillation into the condenser. The ester would then undergo a Fries rearrangement to give 1-(2-hydroxy-4-methylphenyl)-3-methylbut-2-en-1-one (**70c**). While this species is a significant product in the aluminum chloride catalyzed reaction, strong coordination of the (excess) aluminum chloride with both the phenol and side chain oxygen functions prevents cyclization. However, when **70c** is exposed to catalytic bismuth(III) triflate, it is rapidly and quantitatively converted to the ring closed product. Once ring closure occurs, proton transfer and tautomerization would lead to the observed 4-chromanone **71c**.

2.2.12 Conclusion

An efficient bismuth(III) catalyzed tandem reaction was developed to prepare 4-chromanones from electron rich phenols and 3,3-dimethylacrylic acid or *trans*-crotonic acid. The procedure is convenient to perform, product purification was straightforward, and the target heterocycles are isolated in fair to excellent yields. A reasonable selection of substrates was surveyed to define the scope of the reaction. Limitations were predictably associated with deactivating groups on the aromatic nucleus and steric hindrance toward reattachment of the acyl group to the aromatic ring during the Fries rearrangement. Additionally, experiments confirmed that the sequence of events during the reaction involved (1) esterification of the acid by the phenol, (2) Fries rearrangement of the 2-butenyl acylium fragment to the less hindered ortho position and (3) oxa-Michael ring closure of the phenolic OH to the side chain enone of the Fries product.

2.3 Chemistry

General Methods: All reactions were run under dry nitrogen in oven-dried glassware. Reactions were monitored by thin layer chromatography on silica gel GF plates (Analtech, No. 21521). Preparative separations were performed by one of the following methods: (1) preparative thin layer chromatography (PTLC) on 20-cm × 20-cm silica gel GF plates (Analtech, No. 02015) or (2) column chromatography on silica gel (grade 62, 60–200 mesh) containing UV-active phosphor (Sorbent Technologies, No. UV-05) packed into quartz columns. Band elution for all chromatographic methods was monitored using a hand-held UV lamp. Melting points were uncorrected. FT-IR spectra were run as thin films on NaCl disks or as Nujol mulls. Unless otherwise indicated, ^{1}H and ^{13}C NMR spectra were measured in $CDCl_3$ using $(CH_3)_4Si$ as the internal standard; coupling constants (*J*) are given in Hertz. Low-resolution mass spectra (electron impact/direct probe) were obtained at 70 eV. Elemental analyses (±0.4%) were performed by Atlantic Microlabs, Inc., Norcross, GA 30071. All 5-amino-1*H*-pyrazoles were obtained commercially except for ethyl 5-aminopyrazole-3-carboxylate, which was prepared by

the method of Skinner and co-workers.[79] High-resolution mass spectra (HRMS-ESI) were determined using a Thermo LTQ-OrbitrapXL mass spectrometer.

2.3.1 Isoquinolin-1(2*H*)-ones and 1,6-naphthyridin-5(6*H*)-ones

Representative synthesis of β-enaminoesters **2**

A solution of β-ketoester **1** (10 mmol) in 50 mL of benzene was treated with benzylamine (10.5 mmol) and one crystal of *p*-TsOH. The solution was refluxed for 8 h with Dean–Stark removal of H_2O. The reaction was cooled and concentrated under vacuum to give the β-enaminoester as a yellow oil. The *Z* isomer was strongly favored due to intramolecular hydrogen bonding. The product was nearly pure by ^{1}H NMR, but sensitive toward chromatography. It was, therefore, used without further purification.

Methyl (*Z*)-3-(benzylamino)-2-butenoate (2a). IR: 3292, 1653, 1607 cm^{-1}; ^{1}H NMR (300 MHz): δ 8.94 (br s, 1H), 7.36–7.19 (complex m, 5H), 4.54 (s, 1H), 4.42 (d, *J* = 6.6 Hz, 2H), 3.63 (s, 3H), 1.90 (s, 3H); ^{13}C NMR (75 MHz): δ 170.8, 161.9, 138.6, 128.7, 127.3, 126.6, 82.7, 49.9, 46.7, 19.3; ms: *m*/*z* 114 ($M^+-C_7H_7$).

Methyl (*Z*)-3-(benzylamino)-2-pentenoate (**2b**). IR: 3287, 1653, 1606 cm^{-1}; ^{1}H NMR (300 MHz): δ 8.96 (br s, 1H), 7.38–7.18 (complex m, 5H), 4.57 (s, 1H), 4.43 (d, *J* = 6.6 Hz, 2H), 3.64 (s, 3H), 2.23 (q, *J* = 7.1 Hz, 2H), 1.12 (q, *J* = 7.1 Hz, 3H); ^{13}C NMR (75 MHz): δ 171.2, 167.0, 138.7, 128.7, 127.3, 126.7, 80.7, 50.0, 46.3, 25.1, 12.1; ms: *m*/*z* 128 ($M^+-C_7H_7$).

Methyl (*Z*)-3-(benzylamino)-2-hexenoate (2c). IR: 3287, 1655, 1606 cm^{-1}; ^{1}H NMR (300 MHz): δ 8.94 (br s, 1H), 7.37–7.21 (complex m, 5H), 4.55 (s, 1H), 4.42 (d, *J* = 6.6 Hz, 2H), 3.63 (s, 3H), 2.20 (t, *J* = 7.7 Hz, 2H), 1.55 (sextet, *J* = 7.7 Hz, 2H), 0.95 (t, *J* = 7.7 Hz, 3H); ^{13}C NMR (75 MHz): δ 171.1, 165.6, 138.7, 128.7, 127.3, 126.7, 81.8, 49.9, 46.4, 34.2, 21.2, 13.8; ms: *m*/*z* 142 ($M^+-C_7H_7$)

Methyl (*Z*)-3-(benzylamino)-2-octenoate (2d). IR: 3285, 1657, 1606 cm^{-1}; ^{1}H NMR (300 MHz): δ 8.94 (br s, 1H), 7.38–7.22 (complex m, 5H), 4.55 (s, 1H), 4.42 (d, *J* = 6.6 Hz, 2H),

3.63 (s, 3H), 2.18 (t, *J* = 7.1 Hz, 2H), 1.52 (quintet, *J*=7.1 Hz, 2H), 1.30 (m, 4H), 0.87 (t, *J* = 6.6 Hz, 3H); ^{13}C NMR (75 MHz): δ 171.1, 165.9, 138.7, 128.7, 127.3, 126.7, 81.7, 49.9, 46.4, 32.2, 31.4, 27.7, 22.3, 13.7; ms: *m*/*z* 170 ($M^+-C_7H_7$).

Methyl (*Z*)-3-(benzylamino)-5-phenyl-2-pentenoate (2e). IR: 3285, 1653, 1606 cm^{-1}; ^{1}H NMR (300 MHz): δ 8.97 (br s, 1H), 7.38–7.20 (complex m, 8H), 7.13 (d, *J* = 6.6 Hz, 2H), 4.62 (s, 1H), 4.37 (d, *J* = 6.6 Hz, 2H), 3.64 (s, 3H), 2.81 (t, *J* = 7.7 Hz, 2H), 2.48 (t, *J* = 7.7 Hz, 2H); ^{13}C NMR (75 MHz): δ 171.1, 164.8, 140.4, 138.5, 128.8, 128.5, 128.2, 127.4, 126.7, 126.3, 82.0, 50.0, 46.4, 34.5, 34.0; ms: *m*/*z* 204 ($M^+-C_7H_7$).

Methyl (*Z*)-3-(benzylamino)-2,6-heptadienoate (2f). IR: 3286, 1655, 1610 cm^{-1}; ^{1}H NMR (300 MHz): δ 8.95 (br s, 1H), 7.39–7.21 (complex m, 5H), 5.79 (ddt, *J* = 17.0, 9.3, 4.9 Hz, 1H), 5.02 (d, *J* = 17.0 Hz, 1H), 5.00 (d, *J* = 9.3 Hz, 1H), 4.56 (s, 1H), 4.43 (d, *J* = 6.6 Hz, 2H), 3.64 (s, 3H), 2.28 (m, 4H); ^{13}C NMR (75 MHz): δ 171.0, 164.8, 138.6, 136.6, 128.8, 127.4, 126.7, 115.6, 82.0, 50.0, 46.5, 32.0, 31.5; ms: *m*/*z* 154 ($M^+-C_7H_7$).

Methyl (*Z*)-3-(benzylamino)-4-methyl-2-pentenoate (2g). IR: 3281, 1653, 1606 cm^{-1}; ^{1}H NMR (300 MHz): δ 9.07 (br s, 1H), 7.38–7.21 (complex m, 5H), 4.61 (s, 1H), 4.45 (d, *J* = 6.0 Hz, 2H), 3.64 (s, 3H), 2.66 (septet, *J* = 6.6 Hz, 1H), 1.10 (d, *J* = 6.6 Hz, 6H); ^{13}C NMR (75 MHz): δ 171.8, 171.6, 138.8, 128.7, 127.2, 126.2, 78.1, 50.0, 46.0, 28.5, 21.5; ms: *m*/*z* 142 ($M^+-C_7H_7$).

Methyl (*Z*)-3-(methylamino)-2-butenoate (2h). This compound was prepared in 84% yield by a literature procedure,[72] mp 64–66 °C (lit[72] mp 65–67 °C). IR 3310, 1652, 1604 cm^{-1}; ^{1}H NMR (300 MHz): δ 8.46 (br s, 1H), 4.47 (s, 1H), 3.61 (s, 3H), 2.91 (d, *J* = 4.9 Hz, 3H), 1.92 (s, 3H); ^{13}C NMR (75 MHz): δ 170.9, 162.8, 81.4, 49.8, 29.5, 19.1; ms: *m*/*z* 129 (M^+).

2-Fluoro-5-nitrobenzoyl chloride (4). This compound was prepared by refluxing acid **3** (10 mmol) with thionyl chloride (12 mmol) in benzene for 8 h. Removal of the solvent gave a tan solid, mp 59–60 °C. This material was spectroscopically pure and was used without further purification. IR: 1793, 1770, 1626, 1538, 1352 cm^{-1}; ^{1}H NMR (300 MHz): δ 9.02 (dd, *J* =

6.0, 3.0 Hz, 1H), 8.57 (dt, *J* = 8.8, 3.0 Hz, 1H), 7.44 (t, *J* = 9.3 Hz, 1H); ^{13}C NMR (75 MHz): δ 164.2 (d, *J* = 276.8 Hz), 161.3 (d, *J* = 4.9 Hz), 143.9, 131.5 (d, *J* = 11.5 Hz), 129.5, 123.0 (d, *J* = 9.8 Hz), 118.9 (d, *J* = 23.8 Hz).

2-Chloronicotinoyl chloride (7). This compound was prepared by refluxing acid **6** (10 mmol) with thionyl chloride (12 mmol) in benzene for 8 h. Removal of the solvent gave a tan solid, mp 39–42 °C (lit.[144] mp 39–42 °C). The ^{1}H NMR and ^{13}C NMR spectra matched those reported previously[144] and the compound was used without further purification

General cyclization procedure for systems with diactivated aromatic acceptor rings

A solution of enaminoester **2** (0.98 mmol) in 3 mL of purified 1,2-dichloroethane (DCE)[72] was cooled to 10 °C and a solution of **5** (100 mg, 0.49 mmol) in 3 mL of DCE was added. The solution was stirred at 23 °C for 3 h, then cooled to 10 °C and TEA (0.98 mmol, 99 mg, 0.136 mL) in 2 mL of DCE was added. The reaction was heated at reflux until complete (12–18 h). The reaction was cooled and added to saturated aqueous NaCl (10 mL). The organic layer was separated, and the aqueous phase was washed with dichloromethane. The combined organic extracts were washed with aqueous NaCl, dried ($MgSO_4$), filtered, and concentrated under vacuum. The crude product was purified by PTLC eluted with 1:1 ethyl acetate/hexanes containing 1% TEA. The following compounds were prepared by this method.

2-Benzyl-4-methoxycarbonyl-3-methyl-7-nitroisoquinolin-1(2*H*)-one (8a). Yield: 146 mg (0.42 mmol, 85%) as a tan solid, mp 192–194 °C; IR: 1733, 1632, 1614, 1523, 1342 cm^{-1}; ^{1}H NMR (300 MHz): δ 9.13 (d, *J* = 2.7 Hz, 1H), 8.27 (dd, *J* = 9.9, 2.7 Hz, 1H), 7.44–7.31 (complex m, 4H), 7.07 (d, *J* = 6.6 Hz, 2H), 5.50 (s, 2H), 3.96 (s, 3H), 2.51 (s, 3H); ^{13}C NMR (75 MHz): δ 173.1, 167.0, 151.2, 144.2, 143.4, 133.6, 129.6, 128.4, 126.7, 125.8, 125.0, 122.9, 119.6, 118.1, 52.7, 51.4, 18.8; ms: *m*/*z* 261 ($M^{+}-C_7H_7$). Anal. Calcd for $C_{19}H_{16}N_2O_5$: C, 64.77; H, 4.55; N, 7.95. Found: C, 64.90; H, 4.58; N, 7.74.

2-Benzyl-3-ethyl-4-methoxycarbonyl-7-nitroisoquinolin-1(2*H*)-one (8b). Yield: 154 mg (0.42 mmol, 86%) as a tan solid, mp 128–130 °C; IR: 1730, 1630, 1613, 1523, 1354 cm^{-1}; ^1H NMR (300 MHz): δ 9.22 (d, *J* = 2.7 Hz, 1H), 8.28 (dd, *J* = 9.3, 2.7 Hz, 1H), 7.48–7.30 (complex m, 4H), 7.07 (d, *J* = 6.0 Hz, 2H), 5.52 (s, 2H), 3.97 (s, 3H), 2.78 (q, *J* = 7.7 Hz, 2H), 1.40 (t, *J* = 7.7 Hz, 3H); ^{13}C NMR (75 MHz): δ 173.6, 167.0, 155.5, 144.2, 143.5, 134.0, 129.6, 128.5, 126.7, 126.3, 125.1, 123.3, 119.4, 118.2, 52.7, 50.7, 25.5, 13.7; ms: *m*/*z* 275 ($M^+-C_7H_7$). Anal. Calcd for $C_{20}H_{18}N_2O_5$: C, 65.57; H, 4.92; N, 7.65. Found: C, 65.68; H, 4.90; N, 7.53.

2-Benzyl-4-methoxycarbonyl-7-nitro-3-propylisoquinolin-1(2*H*)-one (8c). Yield: 152 mg (0.40 mmol, 82%) as a tan solid, mp 120–121 °C; IR: 1730, 1628, 1614, 1525, 1353 cm^{-1}; ^1H NMR (300 MHz): δ 9.22 (d, *J* = 2.7 Hz, 1H), 8.27 (dd, *J* = 9.3, 2.7 Hz, 1H), 7.45 (d, *J* = 9.3 Hz, 1H), 7.44–7.32 (complex m, 3H), 7.07 (d, *J* = 6.6 Hz, 2H), 5.50 (s, 2H), 3.97 (s, 3H), 2.72 (t, *J* = 7.7 Hz, 2H), 1.80 (sextet, *J* = 7.7 Hz, 2H), 1.04 (t, *J* = 7.7 Hz, 3H); ^{13}C NMR (75 MHz): *δ* 173.5, 167.1, 154.5, 144.2, 143.5, 134.0, 129.6, 128.5, 126.7, 126.3, 125.1, 123.2, 119.6, 118.3, 52.7, 50.8, 34.0, 23.0, 14.3; ms: *m*/*z* 289 ($M^+-C_7H_7$). Anal. Calcd for $C_{21}H_{20}N_2O_5$: C, 66.32; H, 5.26; N, 7.37. Found: C, 66.52; H, 5.59; N, 7.19.

2-Benzyl-4-methoxycarbonyl-7-nitro-3-pentylisoquinolin-1(2*H*)-one (8d). Yield: 148 mg (0.36 mmol, 74%) as a tan solid, mp 122–123 °C; IR: 1733, 1628, 1613, 1523, 1343 cm^{-1}; ^1H NMR (300 MHz): δ 9.18 (d, *J* = 2.7 Hz, 1H), 8.26 (dd, *J* = 9.3, 2.7 Hz, 1H), 7.49 (d, *J* = 9.3 Hz, 1H), 7.41–7.30 (complex m, 3H), 7.08 (d, *J* = 6.6 Hz, 2H), 5.54 (s, 2H), 3.95 (s, 3H), 2.73 (t, *J* = 7.7 Hz, 2H), 1.77 (quintet, *J* = 7.7 Hz, 2H), 1.34 (m, 4H), 0.88 (t, *J* = 6.6 Hz, 3H); ^{13}C NMR (75 MHz): δ 173.4, 167.0, 154.7, 144.1, 143.3, 134.0, 129.4, 128.3, 126.5, 126.1, 125.0, 123.0, 119.4, 118.4, 52.5, 50.7, 31.9, 31.6, 28.9, 21.8, 13.6; ms: *m*/*z* 317 ($M^+-C_7H_7$). Anal. Calcd for $C_{23}H_{24}N_2O_5$: C, 67.65; H, 5.88; N, 6.86. Found: C, 67.91; H, 5.93; N, 6.51.

2-Benzyl-3-(3-butenyl)-4-methoxycarbonyl-7-nitroisoquinolin-1(2*H*)-one (8e). Yield: 130 mg (0.33 mmol, 68%) as a yellow solid, mp 114–116 °C; IR: 1730, 1633, 1614, 1524, 1344 cm^{-1}; ^1H

NMR (300 MHz): δ 9.23 (d, *J* = 2.7 Hz, 1H), 8.29 (dd, *J* = 9.3, 2.7 1H), 7.45 (d, *J* = 9.3 Hz, 1H), 7.44–7.31 (complex m, 3H), 7.07 (d, *J* = 6.6 Hz, 2H), 5.82 (ddt, *J* = 17.0, 9.9, 6.6 Hz, 1H), 5.50 (s, 2H), 5.07 (d, *J* = 17.0 Hz, 1H), 5.06 (d, *J* = 9.9 Hz, 1H), 3.96 (s, 3H), 2.86 (t, *J* = 7.7 Hz, 2H), 2.50 (q, *J* = 7.7 Hz, 2H); ^{13}C NMR (75 MHz): δ 173.4, 166.9, 153.9, 144.2, 143.5, 135.1, 133.9, 129.5, 128.5, 126.7, 126.2, 125.1, 123.2, 119.7, 118.4, 116.7, 52.7, 50.9, 33.0, 31.3; ms: *m*/*z* 301 ($M^+-C_7H_7$). Anal. Calcd for $C_{22}H_{20}N_2O_5$: C, 67.35; H, 5.10; N, 7.14. Found: C, 67.46; H, 5.12; N, 7.07.

2-Benzyl-4-methoxycarbonyl-7-nitro-3-(2-phenylethyl)isoquinolin-1(2*H*)-one (8f). Yield: 175 mg (0.40 mmol, 81%) as a tan solid, mp 188–189 °C; IR: 1729, 1628, 1613, 1522, 1343 cm^{-1}; ^{1}H NMR (300 MHz): δ 9.28 (d, *J* = 2.7 Hz, 1H), 8.32 (dd, *J* = 9.3, 2.7 Hz, 1H), 7.43 (d, *J* = 9.3 Hz, 1H), 7.42–7.23 (complex m, 6H), 7.12 (d, *J* = 6.0 Hz, 2H), 7.05 (d, *J* = 6.0 Hz, 2H), 5.40 (s, 2H), 4.00 (s, 3H), 3.05 (s, 4H); ^{13}C NMR (75 MHz): δ 173.6, 167.1, 153.7, 144.2, 143.8, 139.1, 133.9, 129.7, 128.9, 128.7, 128.1, 127.1, 126.9, 126.5, 125.1, 123.5, 119.8, 118.2, 52.9, 50.9, 35.6, 33.9; ms: *m*/*z* 351 ($M^+-C_7H_7$). Anal. Calcd for $C_{26}H_{22}N_2O_5$: C, 70.59; H, 4.98; N, 6.33. Found: C, 70.66; H, 5.01; N, 6.25.

2-Benzyl-3-isopropyl-4-methoxycarbonyl-7-nitroisoquinolin-1(2*H*)-one (8g). Yield: 56 mg (0.15 mmol, 30%) as a tan solid, mp 170–172 °C; IR: 1730, 1625, 1610, 1524, 1344 cm^{-1}; ^{1}H NMR (300 MHz): δ 9.22 (d, *J* = 2.7 Hz, 1H), 8.27 (dd, *J* = 9.3, 2.7 Hz, 1H), 7.45–7.31 (complex m, 4H), 7.10 (d, *J* = 6.6 Hz, 2H), 5.52 (s, 2H), 3.96 (s, 3H), 3.20 (septet, *J* = 7.1 Hz, 1H), 1.42 (d, *J* = 7.1 Hz, 6H); ^{13}C NMR (75 MHz): δ 174.6, 167.3, 158.1, 144.8, 143.4, 134.3, 129.6, 128.46, 128.43, 126.6, 125.6, 124.9, 123.0, 118.5, 52.6, 51.6, 31.8, 29.6, 20.6; ms: *m*/*z* 289 ($M^+-C_7H_7$). Anal. Calcd for $C_{21}H_{20}N_2O_5$: C, 66.32; H, 5.26; N, 7.37. Found: C, 66.45; H, 5.30; N, 7.23.

2,3-Dimethyl-4-methoxycarbonyl-7-nitroisoquinolin-1(2*H*)-one (8h). Yield: 115 mg (0.42 mmol, 85%) as a yellow solid, mp 298–300 °C (darkens); IR: 1725, 1626, 1611, 1523,

1340 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 8.85 (d, *J* = 2.7 Hz, 1H), 8.49 (dd, *J* = 9.3, 2.7 Hz, 1H), 8.08 (d, *J* = 9.3 Hz, 1H), 3.83 (s, 3H), 3.82 (s, 3H), 2.50 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 172.0, 167.0, 151.9, 144.6, 142.8, 126.4, 124.8, 121.4, 119.3, 118.7, 52.3, 35.7, 19.3; ms: *m*/*z* 276 (M^+). Anal. Calcd for $C_{13}H_{12}N_2O_5$: C, 56.52; H, 4.35; N, 10.14. Found: C, 56.57; H, 4.35; N, 10.08.

General cyclization procedure for systems with monoactivated aromatic acceptor rings

A 15-mL, screw-top, pressure vessel (ChemGlass, No CG-1880-01) was charged with enaminoester **2** (2.52 mmol) and 2 mL of purified 1,4-dioxane. The solution was cooled to 15 °C, and a solution of 2-fluorobenzoyl chloride (**6**) (200 mg, 1.26 mmol) in 2 mL of dioxane was added. The reaction was stirred at 23 °C for 3 h, then cooled to 15 °C and DBU (2.52 mmol, 383 mg, 0.376 mL) in 1 mL of dioxane was added. The reaction was sealed under nitrogen, and heated to 130 °C for 3 h. The reaction was cooled and concentrated under vacuum. The residue was dissolved in dichloromethane, washed with water and aqueous NaCl, dried ($MgSO_4$), filtered, and concentrated under vacuum. The resulting product was purified on a 20 cm × 2 cm silica gel column eluted with increasing concentrations of ethyl acetate in hexanes. The following compounds were prepared:

2-Benzyl-4-methoxycarbonyl-3-methylisoquinolin-1(2*H*)-one (9a). Yield: 220 mg (0.72 mmol, 57%) as a white solid, mp 113–115 °C; IR: 1727, 1618, 1602 cm^{-1}; ^1H NMR (300 MHz): δ 8.46 (dd, *J* = 8.2, 1.6 Hz, 1H), 7.53 (td, *J* = 7.1, 1.6 Hz, 1H), 7.42–7.24 (complex m, 5H), 7.08 (d, *J* = 6.6 Hz, 2H), 5.44 (s, 2H), 3.96 (s, 3H), 2.43 (s, 3H); ^{13}C NMR (75 MHz): δ 174.2, 168.2, 149.8, 140.8, 134.6, 132.7, 129.2, 127.9, 126.7, 126.3, 125.1, 124.0, 118.2, 116.2, 52.4, 50.6, 18.6; ms: *m*/*z* 216 ($M^+-C_7H_7$). Anal. Calcd for $C_{19}H_{17}NO_3$: C, 74.27; H, 5.54; N, 4.56. Found: C, 74.19; H, 5.55; N, 4.51.

2-Benzyl-3-ethyl-4-methoxycarbonylisoquinolin-1(2*H*)-one (9b). Yield: 210 mg (0.66 mmol, 52%) as a white solid, mp 108-109 ºC; IR: 1727, 1618, 1600 cm^{-1}; ^1H NMR (300 MHz): δ 8.46

(d, *J* = 8.2 Hz, 1H), 7.51 (t, *J* = 7.1 Hz, 1H), 7.40-7.25 (complex m, 5H), 7.07 (d, *J* = 7.1 Hz, 2H), 5.46 (s, 2H), 3.96 (s, 3H), 2.76 (q, *J* = 7.1 Hz, 2H), 1.37 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (75 MHz): δ 174.7, 168.2, 154.3, 140.8, 135.1, 132.7, 129.3, 128.0, 126.9, 126.6, 125.2, 124.0, 117.9, 116.5, 52.5, 50.0, 25.3, 13.8; ms: *m/z* 230 (M^+-C_7H_7). Anal. Calcd for $C_{20}H_{19}NO_3$: C, 74.77; H, 5.92; N, 4.36. Found: C, 74.91; H, 5.94; N, 4.27.

2-Benzyl-4-methoxycarbonyl-3-propylisoquinolin-1(2H)-one (9c). Yield: 245 mg (0.73 mmol, 58%) as a white solid, mp 168-169 °C; IR: 1727, 1619, 1600 cm^{-1}; ^{1}H NMR (300 MHz): δ 8.46 (d, *J* = 8.2 Hz, 1H), 7.51 (t, *J* = 6.6 Hz, 1H), 7.40-7.25 (complex m, 5H), 7.07 (d, *J* = 7.1 Hz, 2H), 5.44 (s, 2H), 3.96 (s, 3H), 2.69 (t, *J* = 7.7 Hz, 2H), 1.79 (sextet, *J* = 7.7 Hz, 2H), 1.01 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (75 MHz): δ 174.6, 168.2, 153.3, 140.8, 135.1, 132.7, 129.3, 128.1, 127.0, 126.7, 125.3, 124.1, 118.2, 116.5, 52.5, 50.2, 33.9, 23.1, 14.3; ms: *m/z* 244 (M^+-C_7H_7). Anal. Calcd for $C_{21}H_{21}NO_3$: C, 75.22; H, 6.27; N, 4.18. Found: C, 75.31; H, 6.30; N, 4.05.

2-Benzyl-4-methoxycarbonyl-3-pentylisoquinolin-1(2*H*)-one (9d). Yield: 229 mg (0.63 mmol, 50%) as a white solid, mp 92-93 °C; IR: 1727, 1619, 1600 cm^{-1}; ^{1}H NMR (300 MHz): δ 8.47 (d, *J* = 7.7 Hz, 1H), 7.52 (t, *J* = 7.1 Hz, 1H), 7.41-7.27 (complex m, 5H), 7.07 (d, *J* = 6.6 Hz, 2H), 5.44 (s, 2H), 3.96 (s, 3H), 2.69 (t, *J* = 7.7 Hz, 2H), 1.75 (quintet, *J* = 7.1 Hz, 2H), 1.60 (m, 4H), 0.88 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (75 MHz): δ 174.6, 168.2, 153.5, 140.8, 135.1, 132.7, 129.3, 128.1, 127.0, 126.7, 125.3, 124.1, 118.2, 116.5, 52.5, 50.2, 31.9, 31.8, 29.2, 22.1, 13.8; ms: *m/z* 272 (M^+-C_7H_7). Anal. Calcd for $C_{23}H_{25}NO_3$: C, 76.03; H, 6.89; N, 3.86. Found: C, 75.97; H, 6.93; N, 3.69.

2-Benzyl-3-(3-butenyl)-4-methoxycarbonylisoquinolin-1(2*H*)-one (9e). Yield: 262 mg (0.76 mmol, 60%) as a white solid, mp 106-107 °C; IR: 1726, 1618, 1601 cm^{-1} ; ^{1}H NMR (300 MHz): δ 8.48 (dd, *J* = 6.6, 1.6 Hz, 1H), 7.53 (t, *J* = 7.1 Hz, 1H), 7.40-7.28 (complex m, 5H), 7.07 (d, *J* = 6.6 Hz, 2H), 5.82 (ddt, *J* = 17.0, 10.4, 6.6 Hz, 1H), 5.42 (s, 2H), 5.06 (d, *J* = 17.0 Hz, 1H), 5.05 (d, *J* = 10.4 Hz, 1H), 3.96 (s, 3H), 2.83 (t, *J* = 6.6 Hz, 2H), 2.49 (q, *J* = 6.6 Hz, 2H); ^{13}C NMR

(75 MHz): δ 174.6, 168.1, 152.6, 140.8, 135.7, 135.0, 132.8, 129.4, 128.1, 127.0, 126.7, 125.3, 124.2, 118.2, 116.5, 116.4, 52.5, 50.3, 33.3, 31.2; ms: *m/z* 256 (M^+). Anal. Calcd for $C_{22}H_{21}NO_3$: C, 76.08; H, 6.05; N, 4.03. Found: C, 76.01; H, 6.08; N, 3.98.

2-Benzyl-4-methoxycarbonyl-3-(2-phenylethyl)isoquinolin-1(2*H*)-one (9f). Yield: 365 mg (0.92 mmol, 73%) as a white solid, mp 154-156 °C; IR: 1724, 1616, 1600 cm^{-1} ; ^1H NMR (300 MHz): δ 8.48 (dd, *J* = 6.6, 1.1 Hz, 1H), 7.53 (t, *J* = 8.2 Hz, 1H), 7.40-7.19 (complex m, 9H), 7.12 (d, *J* = 6.6 Hz, 2H), 7.06 (d, *J* = 6.6 Hz, 2H), 5.40 (s, 2H), 3.98 (s, 3H), 3.03 (s, 3H); ^{13}C NMR (75 MHz): δ 174.6, 168.2, 152.5, 140.9, 138.5, 135.0, 132.8, 129.4, 128.8, 128.1, 127.0, 126.8, 126.7, 125.3, 124.2, 118.3, 116.5, 52.6, 50.2, 35.6, 33.9 (one aromatic C was unresolved); ms: *m/z* 306 (M^+-C_7H_7). Anal. Calcd for $C_{26}H_{23}NO_3$: C, 78.59; H, 5.79; N, 3.53. Found: C, 78.55; H, 5.80; N, 3.49.

2-Benzyl-3-isopropyl-4-methoxycarbonylisoquinolin-1(2*H*)-one (9g). Yield: 126 mg (0.38 mmol, 30%) as a white solid, mp 145-147 °C; IR: 1729, 1616, 1602 cm^{-1}; ^1H NMR (300 MHz): δ 8.43 (dd, *J* = 7.7, 1.1 Hz, 1H), 7.52 (td, *J* = 7.7, 1.1 Hz, 1H), 7.42-7.23 (complex m, 5H), 7.10 (d, *J* = 6.6 Hz, 2H), 5.47 (s, 2H), 3.95 (s, 3H), 3.19 (septet, *J* = 6.6 Hz, 1H), 1.40 (d, *J* = 6.6 Hz, 6H); ^{13}C NMR (75 MHz): δ 175.6, 168.5, 156.7, 141.4, 135.5, 132.7, 129.3, 128.0, 126.7, 126.1, 125.1, 123.9, 116.7, 52.4, 51.0, 31.7, 20.7 (1 aromatic C unresolved); ms: *m/z* 244 (M^+). Anal. Calcd for $C_{21}H_{21}NO_3$: C, 75.22; H, 6.27; N, 4.18. Found: C, 75.28; H, 6.24; N, 4.16.

2,3-Dimethyl-4-methoxycarbonylisoquinolin-1(2*H*)-one (9h). Yield: 154 mg (0.66 mmol, 53%) as a white solid, mp 156-157 °C; IR: 1721, 1610, 1601 cm^{-1}; ^1H NMR (300 MHz): δ 8.41 (dd, *J* = 8.2, 1.6 Hz, 1H), 7.64 (td, *J* = 8.2, 1.6 Hz, 1H), 7.47 (d, *J* = 8.8 Hz, 1H), 7.36 (t, *J* = 7.1 Hz, 1H), 3.94 (s, 3H), 3.74 (s, 3H), 2.50 (s, 3H); ^{13}C NMR (75 MHz): δ 174.2, 168.4, 149.6, 141.1, 132.6, 126.9, 126.3, 124.0, 118.1, 115.3, 52.5, 34.7, 19.4; ms: *m/z* 231 (M^+). Anal. Calcd for $C_{13}H_{13}NO_3$: C, 67.53; H, 5.63; N, 6.06. Found: C, 67.66; H, 5.65; N, 5.99.

General cyclization procedure for systems with 2-chloropyridine systems. These reactions were run as above using enaminoester **2** (3.42 mmol) and **7** (200 mg, 1.14 mmol) in purified DCE. The cyclization was completed by adding TEA (2.28 mmol, 230 mg, 0.317 mL) and heating at 130 °C for 8 h in a pressure tube. In each case, work-up and purification by PTLC, eluted with 1:1 ethyl acetate/hexanes containing 1% TEA, afforded the final product. [Note: DBU (2.28 mmol) was also used in the cyclization step, but the yields were lower.] The following compounds were prepared by this method.

6-Benzyl-8-methoxycarbonyl-7-methyl-1,6-naphthyridin-5(6*H*)-one (10a). Yield: 246 mg (0.80 mmol, 70%) as a tan solid, mp 143-145 °C; IR: 1727, 1617, 1600 cm^{-1}; ^1H NMR (400 MHz): δ 8.76 (dd, *J* = 8.0, 2.0 Hz, 1H), 8.70 (dd, *J* = 4.5, 2.0 Hz, 1H), 7.38 (dd, *J* = 7.8, 4.5 Hz, 1H), 7.35-7.24 (complex m, 3H), 7.04 (d, *J* = 6.6 Hz, 2H), 5.89 (br s, 2H), 3.94 (s, 3H), 2.47 (s, 3H); ^{13}C NMR (100 MHz): δ 174.5, 167.7, 152.6, 151.4, 150.4, 136.2, 136.1, 129.0, 127.6, 125.8, 120.8, 120.4, 119.1, 52.6, 48.0, 18.7; ms: *m/z* 217 (M^+-C_7H_7). Anal. Calcd for $C_{18}H_{16}N_2O_3$: C, 70.13; H, 5.19; N, 9.09. Found: C, 70.18; H, 5.20; N, 9.04.

6-Benzyl-7-ethyl-8-methoxycarbonyl-1,6-naphthyridin-5(6*H*)-one (10b). Yield: 272 mg (0.84 mmol, 74%) as a tan solid, mp 156-158 °C; IR: 1727, 1617, 1600 cm^{-1} ; ^1H NMR (400 MHz): δ 8.74 (dd, *J* = 7.8, 2.0 Hz, 1H), 8.67 (dd, *J* = 4.5, 2.0 Hz, 1H), 7.35 (dd, *J* = 8.0, 4.5 Hz, 1H), 7.32-7.22 (complex m, 3H), 7.01 (d, *J* = 6.8 Hz, 2H), 5.79 (br s, 2H), 3.94 (s, 3H), 2.77 (q, *J* = 7.6 Hz, 2H), 1.34 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (100 MHz): δ 174.7, 167.5, 156.0, 152.5, 150.3, 136.6, 136.0, 128.9, 127.5, 125.5, 120.8, 120.3, 118.7, 52.5, 47.4, 25.1, 13.8; ms: *m/z* 231 (M^+-C_7H_7). Anal. Calcd for $C_{19}H_{18}N_2O_3$: C, 70.81; H, 5.59; N, 8.70. Found: C, 70.88; H, 5.61; N, 8.57.

6-Benzyl-8-methoxycarbonyl-7-propyl-1,6-naphthyridin-5(6*H*)-one (10c). Yield: 291 mg (0.87 mmol, 76%) as a tan solid, mp 162-163 °C; IR: 1727, 1617, 1600 cm^{-1}; ^1H NMR (400 MHz): δ 8.74 (dd, *J* = 8.0, 2.0 Hz, 1H), 8.67 (dd, *J* = 4.5, 2.0 Hz, 1H), 7.35 (dd, *J* = 7.8, 4.5 Hz, 1H), 7.36-7.26 (complex m, 3H), 7.02 (d, *J* = 6.8 Hz, 2H), 5.87 (br s, 2H), 3.94 (s, 3H), 2.70 (t, *J*

= 8.2 Hz, 2H), 1.74 (sextet, *J* = 7.4 Hz, 2H), 1.01 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz): δ 174.7, 167.6, 154.9, 152.5, 150.3, 136.7, 136.1, 128.9, 127.6, 125.7, 120.9, 120.3, 118.9, 52.5, 47.6, 33.7, 23.2, 14.4; ms: *m/z* 245 (M^+-C_7H_7). Anal. Calcd for $C_{20}H_{20}N_2O_3$: C, 71.43; H, 5.95; N, 8.33. Found: C, 71.39; H, 5.92; N, 8.29.

6-Benzyl-8-methoxycarbonyl-7-pentyl-1,6-naphthyridin-5(6*H*)-one (10d). Yield: 290 mg (0.80 mmol, 70%) as a tan solid, mp 165-166 °C; IR: 1728, 1619, 1605 cm^{-1}; ^{1}H NMR (400 MHz): δ 8.74 (dd, *J* = 8.0, 4.5 Hz, 1H), 8.67 (dd, *J* = 4.5, 2.0 Hz, 1H), 7.35 (dd, *J* = 8.0, 4.5 Hz, 1H), 7.33-7.23 (complex m, 3H), 7.02 (d, *J* = 6.8 Hz, 2H), 5.88 (br s, 2H), 3.93 (s, 3H), 2.71 (t, *J* = 8.2 Hz, 2H), 1.71 (quintet, *J* = 7.4 Hz, 2H), 1.38 (m, 4H), 0.89 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (100 MHz): δ 174.6, 167.6, 155.1, 152.5, 150.3, 136.6, 136.0, 128.9, 127.5, 125.6, 120.8, 120.3, 118.8, 52.4, 47.6, 31.8, 31.6 29.2, 22.0, 13.8; ms: *m/z* 273 (M^+-C_7H_7). Anal. Calcd for $C_{22}H_{24}N_2O_3$: C, 72.53; H, 6.59; N, 7.69. Found: C, 72.61; H, 6.59; N, 7.63.

6-Benzyl-7-(3-butenyl)-8-methoxycarbonyl-1,6-naphthyridin-5(6*H*)-one (10e). Yield: 278 mg (0.80 mmol, 70%) as a tan solid, mp 135-136 °C; IR: 1727, 1617, 1600 cm^{-1}; ^{1}H NMR (400 MHz): δ 8.75 (d, *J* = 7.8 Hz, 1H), 8.69 (d, *J* = 4.3 Hz, 1H), 7.37 (dd, *J* = 7.8, 4.5 Hz, 1H), 7.34-7.23 (complex m, 3H), 7.02 (d, *J* = 6.8 Hz, 2H), 5.89 (br s, 2H), 5.81 (ddt, *J* = 16.8, 10.1, 6.4 Hz, 1H), 5.06 (d, *J* = 16.6 Hz, 1H), 5.05 (d, *J* = 10.3 Hz, 1H), 3.94 (s, 3H), 2.84 (t, *J* = 8.0 Hz, 2H), 2.44 (q, *J* = 7.6 Hz, 2H); ^{13}C NMR (100 MHz): δ 174.7, 167.5, 154.3, 152.6, 150.4, 136.6, 136.2, 135.7, 129.0, 127.6, 125.7, 120.9, 120.4, 119.1, 116.3, 52.5, 47.7, 33.3, 31.0; ms: *m/z* 257 (M^+-C_7H_7). Anal. Calcd for $C_{21}H_{20}N_2O_3$: C, 72.41; H, 5.75; N, 8.05. Found: C, 72.29; H, 5.77; N, 7.99.

6-Benzyl-8-methoxycarbonyl-7-(2-phenylethyl)-1,6-naphthyridin-5(6H)-one (10f). Yield: 327 mg (0.82 mmol, 72%) as a tan solid, mp 141-142 °C; IR: 1726, 1620, 1601 cm^{-1}; ^{1}H NMR (400 MHz): δ 8.77 (d, *J* = 7.8 Hz, 1H), 8.70 (d, *J* = 4.5 Hz, 1H), 7.39 (dd, *J* = 7.8, 4.5 Hz, 1H), 7.34-7.21 (complex m, 6H), 7.12 (d, *J* = 7.2 Hz, 2H), 7.01 (d, *J* = 7.0 Hz, 2H), 5.87 (br s, 2H), 3.96

(s, 3H), 3.04 (m, 2H), 2.97 (m, 2H); ^{13}C NMR (100 MHz): δ 174.8, 167.6, 154.2, 152.6, 150.4, 139.6, 136.6, 136.2, 129.0, 128.8, 128.1, 127.7, 126.8, 125.7, 121.0, 120.5, 119.1, 52.6, 47.7, 35.7, 33.8; ms: *m/z* 307 (M^+-C_7H_7). Anal. Calcd for $C_{25}H_{22}N_2O_3$: C, 75.38; H, 5.53; N, 7.04. Found: C, 75.41; H, 5.50; N, 6.97.

6-Benzyl-7-isopropyl-8-methoxycarbonyl-1,6-naphthyridin-5(6*H*)-one (10g). No naphthyridinone product was formed in this reaction.

6,7-Dimethyl-8-methoxycarbonyl-1,6-naphthyridin-5(6*H*)-one (10h). Yield: 222 mg (0.96 mmol, 84%) as a tan solid, mp 189-191 C; IR: 1727, 1617, 1600 cm^{-1}; ^{1}H NMR (400 MHz): δ 8.71 (dd, *J* = 4.5, 2.1 Hz, 1H), 8.68 (dd, *J* = 8.0, 2.1 Hz, 1H), 7.33 (dd, *J* = 7.8, 4.5 Hz, 1H), 3.92 (s, 3H), 3.94 (s, 3H), 2.57 (s, 3H); ^{13}C NMR (100 MHz): δ 174.2, 167.8, 152.1, 151.4, 150.2, 136.0, 120.9, 120.0, 118.5, 52.5, 32.4, 19.2; ms: *m/z* 232 (M^+). Anal. Calcd for $C_{12}H_{12}N_2O_3$: C, 62.07; H, 5.17; N, 12.07. Found: C, 62.21; H, 5.21; N, 11.94.

2.3.2 Pyrazoloquinazolinones and pyrazolopyridopyrimidinones

Representative procedure for the pyrazolo[1,5-*a*]quinazolin-5(4*H*)-one synthesis: To a cooled (-10 °C) mixture containing 5-amino-1*H*-pyrazole (0.65 mmol) and potassium carbonate (1.00 mmol) in 3.0 mL of anhydrous DMF was added dropwise a solution of the acid chloride (0.50 mmol) in 2.0 mL of DMF. The reaction was stirred at -10 °C for 15 minutes, and then gradually warmed to room temperature. After stirring at room temperature for 15 minutes, TLC indicated that acylation of the amino group was complete. The reaction was then immersed in a preheated oil bath at 140-145 °C until the ring closure was complete (30 min-1h). The reaction mass was cooled to room temperature and concentrated to dryness under vacuum. The crude product was slurried in deionized water, filtered, and the resulting solid was washed with methanol:ether (2:1). Alternatively, some cases required column chromatography, which was done on silica using methanol:dichloromethane (1:9) as the eluent [ethanol:dichloromethane (1:9) was used for the product having the ethyl ester].

7-Nitropyrazolo[1,5-*a*]quinazolin-5(4*H*)-one (**15a**). Yield: 94 mg (0.41 mmol, 82%) as a yellow solid, mp > 300 °C; IR (Nujol mull): 3149, 1711 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 13.0 (br s, 1H), 8.94 (d, *J* = 2.9 Hz, 1H), 8.49 (dd, *J* = 9.6, 2.8 Hz, 1H), 8.07 (d, *J* = 1.8 Hz, 1H), 7.53 (d, *J* = 9.6 Hz, 1H), 6.26 (d, *J* = 1.8 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 155.5, 146.1, 144.6, 142.8, 140.8, 129.0, 125.2, 118.4, 111.7, 89.8; MS: *m/z* 230 (M^+). *Anal*. Calcd for $C_{10}H_6N_4O_3$: C, 52.17; H, 2.61; N, 24.35. Found: C, 52.04; H, 2.54; N, 24.47.

2-Methyl-7-nitropyrazolo[1,5-*a*]quinazolin-5(4*H*)-one (**15b**). Yield: 95 mg (0.39 mmol, 78%) as a orange solid, mp > 300 °C; IR (Nujol mull): 3154, 1650 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.92 (s, 1H), 7.99 (d, *J* = 9.4 Hz, 1H), 7.14 (d, *J* = 9.5 Hz, 1H), 5.84 (s, 1H), 2.30 (s, 3H) (NH not observed); ^{13}C NMR (100 MHz, DMSO-d_6): δ 157.0, 154.2, 153.6, 153.2, 135.8, 126.6, 125.4, 124.7, 110.6, 92.5, 15.1; MS: *m/z* 244 (M^+). *Anal*. Calcd for $C_{11}H_8N_4O_3$: C, 54.10; H, 3.28; N, 22.95. Found: C, 54.01; H, 3.24; N, 23.02.

2-Cyclopropyl-7-nitropyrazolo[1,5-*a*]quinazolin-5(4*H*)-one (15c). Yield: 102 mg (0.38 mmol, 76%) as a red solid, mp > 300 °C; IR (Nujol mull): 3213, 1665 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.77 (s, 1H), 8.37 (d, *J* = 8.8 Hz, 1H), 7.93 (d, *J* = 9.1 Hz, 1H), 5.24 (s, 1H), 1.89 (m, 1H), 0.90 (dm, *J* = 10.8 Hz, 2H), 0.75 (dm, *J* = 5.3 Hz, 2H) (NH not observed); ^{13}C NMR (100 MHz, DMSO-d_6): δ 163.8, 160.0, 153.6, 142.2, 141.6, 126.3, 124.8, 118.6, 114.5, 86.8, 10.5, 8.6; MS: *m/z* 270 (M^+). *Anal*. Calcd for $C_{13}H_{10}N_4O_3$: C, 57.78; H, 3.70; N, 20.74. Found: C, 57.69; H, 3.63; N, 20.84.

2-(4-Methylphenyl)-7-nitropyrazolo[1,5-*a*]quinazolin-5(4*H*)-one (15d). Yield: 125 mg (0.39 mmol, 78%) as a yellow solid, mp > 300 °C; IR (Nujol mull): 3579, 1687 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.81 (s, 1H), 8.54 (d, *J* = 9.0 Hz, 1H), 8.20 (d, *J* = 9.0 Hz, 1H), 7.85 (d, *J* = 7.6 Hz, 2H), 7.27 (d, *J* = 7.8 Hz, 2H), 6.21 (s, 1H), 2.36 (s, 3H) (NH not observed); ^{13}C NMR (100 MHz, DMSO-d_6): δ 160.9, 154.7, 143.4, 141.6, 138.5, 130.5, 129.7, 129.6, 128.1, 126.2,

124.6, 118.3, 115.6, 87.4, 21.4; MS: *m/z* 320 (M^+). *Anal.* Calcd for $C_{17}H_{12}N_4O_3$: C, 63.75; H, 3.75; N, 17.50. Found: C, 63.67; H, 3.71; N, 17.62.

Ethyl 7-nitro-5-oxo-4,5-dihydropyrazolo[1,5-*a*]quinazoline-2-carboxylate (15e). Yield: 139 mg (0.46 mmol, 92%) as a maroon powder, mp >300 ºC; IR: 3149, 1716, 1656 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 8.98 (s, 1H), 8.09 (d, *J* = 9.3 Hz, 1H), 7.28 (d, *J* = 9.5 Hz, 1H), 6.45 (s, 1H), 4.35 (q, *J* = 7.1 Hz, 2H), 1.36 (t, *J* = 7.1 Hz, 3H) (NH not observed); ^{13}C NMR (100 MHz, DMSO-d_6): δ 163.4, 157.7, 153.5, 153.4, 147.1, 136.8, 126.5, 126.1, 125.2, 110.6, 94.2, 60.9, 14.7; MS: *m/z* 302 (M^+). *Anal.* Calcd for $C_{13}H_{10}N_4O_5$: C, 51.66; H, 3.31; N, 18.54. Found: C, 51.84; H, 3.37; N, 18.39.

7-Nitro-5-oxo-4,5-dihydropyrazolo[1,5-*a*]quinazoline-3-carbonitrile (15f). Yield: 112 mg (0.44 mmol, 88%) as a yellow solid, mp > 300 °C; IR (Nujol mull): 3370, 2217, 1662 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 8.97 (s, 1H), 8.30 (s, 1H), 8.23 (d, *J* = 9.1 Hz, 1H), 7.47 (d, *J* = 9.3 Hz, 1H) (NH not observed); ^{13}C NMR (100 MHz, DMSO-d_6): δ 156.9, 155.2, 153.9, 146.9, 138.9, 126.4, 126.3, 125.4, 116.3, 112.7, 75.8; MS: *m/z* 255 (M^+). *Anal.* Calcd for $C_{11}H_5N_5O_3$: C, 51.76; H, 1.96; N, 27.45. Found: C, 51.64; H, 1.94; N, 27.63.

7-Nitro-2-(thiophen-2-yl)pyrazolo[1,5-*a*]quinazolin-5(4*H*)-one (15g). Yield: 125 mg (0.40 mmol, 80%) as a yellow solid, mp > 300 °C; IR (Nujol mull): 3572, 1671 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 8.81 (s, 1H), 8.46 (dd, *J* = 8.8, 2.2 Hz, 1H), 8.08 (d, *J* = 9.0 Hz, 1H), 7.55 (d, *J* = 4.4 Hz, 2H), 7.14 (t, *J* = 4.4 Hz, 1H), 6.01 (s, 1H) (NH not observed); ^{13}C NMR (100 MHz, DMSO-d_6): δ 163.0, 152.7, 150.3, 143.0, 141.4, 137.4, 128.2, 126.9, 126.3, 125.8, 124.7, 118.9, 115.2, 87.5; MS: *m/z* 312 (M^+). *Anal.* Calcd for $C_{14}H_8N_4O_3S$: C, 53.85; H, 2.56; N, 17.95. Found: C, 53.78; H, 2.51; N, 18.05.

Pyrazolo[1,5-*a*]quinazolin-5(4*H*)-one (**15h**). Yield: 75 mg (0.40 mmol, 81%) as a white solid, mp 270-271 °C; IR (Nujol mull): 3138, 1690 cm^{-1}; ^1H NMR(400 MHz, DMSO-d_6): δ 12.2 (s, 1H), 8.15 (d, *J* = 8.0 Hz, 1H), 8.09 (d, *J* = 8.2 Hz, 1H), 7.89 (t, *J* = 8.0 Hz, 1H), 7.80 (s, 1H), 7.50

(t, *J* = 7.8 Hz, 1H), 5.92 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 158.9, 142.6, 139.0, 137.9, 135.5, 128.7, 125.8, 116.6, 114.8, 89.0; MS: *m/z* 185 (M^+). *Anal.* Calcd for $C_{10}H_7N_3O$: C, 64.86; H, 3.78; N, 22.70. Found: C, 64.88; H, 3.77; N, 22.66.

2-Methylpyrazolo[1,5-*a*]quinazolin-5(4*H*)-one (15i). Yield: 75 mg (0.37 mmol, 75%) as a white solid, mp 287-288 °C (lit[75] mp 288-289 °C); IR (Nujol mull): 3175, 1669 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.1 (s, 1H), 8.12 (d, *J* = 8.1 Hz, 1H), 7.61 (t, *J* = 7.7 Hz, 1H), 7.32 (d, *J* = 8.5 Hz, 1H), 7.11 (t, *J* = 7.5 Hz, 1H), 5.82 (s, 1H), 2.31 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 156.3, 154.1, 146.0, 143.0, 133.8, 127.7, 120.1, 118.7, 111.9, 87.4, 14.9; MS: *m/z* 199 (M^+). *Anal.* Calcd for $C_{11}H_9N_3O$: C, 66.33; H, 4.54; N, 21.11. Found: C, 66.30; H, 4.54; N, 21.07.

2-Cyclopropylpyrazolo[1,5-*a*]quinazolin-5(4*H*)-one (15j). Yield: 89 mg (0.39 mmol, 79%) as a white solid, mp 298-299 °C; IR (Nujol mull): 3179, 1694 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.1 (s, 1H), 8.16 (d, *J* = 8.0 Hz, 1H), 7.73 (t, *J* = 7.7 Hz, 1H), 7.37 (d, *J* = 8.4 Hz, 1H), 7.24 (t, *J* = 7.6 Hz, 1H), 5.82 (s, 1H), 2.03 (m, 1H), 1.00 (d, *J* = 7.9 Hz, 2H), 0.85 (d, *J* = 5.2 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 161.0, 155.6, 143.0, 140.0, 134.9, 128.0, 121.6, 116.3, 112.0, 84.1, 10.3, 9.2; MS: *m/z* 225 (M^+). *Anal.* Calcd for $C_{13}H_{11}N_3O$: C, 69.33; H, 4.89; N, 18.67. Found: C, 69.27; H, 4.91; N, 18.59.

2-(4-Methylphenyl)pyrazolo[1,5-*a*]quinazolin-5(4*H*)-one (15k). Yield: 105 mg (0.38 mmol, 77%) as a white solid, mp >300 °C; IR (Nujol mull): 3177, 1684 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.3 (s, 1H), 8.22 (d, *J* = 7.9 Hz, 1H), 7.94 (d, *J* = 7.8 Hz, 2H), 7.77 (t, *J* = 7.8 Hz, 1H), 7.43 (d, *J* = 8.4 Hz, 1H), 7.32 (d, *J* = 7.9 Hz, 2H), 7.28 (t, *J* = 7.7 Hz, 1H), 6.55 (s, 1H), 2.38 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 156.0, 155.4, 143.7, 140.2, 139.2, 135.1, 130.0, 129.8, 128.0, 126.8, 121.8, 116.5, 112.2, 84.5, 21.4; MS: *m/z* 275 (M^+). *Anal.* Calcd for $C_{17}H_{13}N_3O$: C, 74.18; H, 4.73; N, 15.27. Found: C, 74.13; H, 4.78; N, 15.18.

Ethyl 5-oxo-4,5-dihydropyrazolo[1,5-*a*]quinazoline-2-carboxylate (15l). Yield 116 mg (0.45 mmol, 90%) as a white solid, mp 282-283 °C; IR (Nujol mull): 3129, 1718, 1692 cm^{-1}; ^{1}H NMR

(400 MHz, DMSO-d_6): δ 12.4 (s, 1H), 8.17 (apparent t, J = 8.3 Hz, 2H), 7.94 (t, J = 7.6 Hz, 1H), 7.59 (t, J = 7.6 Hz, 1H), 6.27 (s, 1H), 4.35 (q, J = 7.1 Hz, 2H), 1.34 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 161.8, 158.6, 144.9, 139.9, 137.4, 135.7, 128.7, 127.1, 117.8, 115.4, 90.7, 61.2, 14.6; MS: *m/z* 257 (M^+). *Anal.* Calcd for $C_{13}H_{11}N_3O_3$: C, 64.10; H, 4.28; N, 16.34. Found: C, 64.04; H, 4.25; N, 16.19.

5-Oxo-4,5-dihydropyrazolo[1,5-*a*]quinazoline-3-carbonitrile (15m). Yield: 97 mg (0.46 mmol, 93%) as a white solid, mp >300 °C; IR (Nujol mull): 3093, 2213, 1699 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.06 (d, J = 7.8 Hz, 1H), 7.97 (s, 1H), 7.93 (d, J = 8.1 Hz, 1H), 7.68 (t, J = 7.6 Hz, 1H), 7.37 (t, J = 7.5 Hz, 1H) (NH not observed); ^{13}C NMR (100 MHz, DMSO-d_6): δ 166.1, 154.5, 143.8, 137.6, 132.1, 128.4, 124.5, 119.1, 117.0, 113.9, 74.1; MS: *m/z* 210 (M^+). *Anal.* Calcd for $C_{11}H_6N_4O$: C, 62.86; H, 2.86; N, 26.67. Found: C, 62.79; H, 2.81; N, 26.65.

Pyrazolo[1,5-*a*]pyrido[3,2-*e*]pyrimidin-5(4*H*)-one (16a). Yield: 61 mg (0.33 mmol, 66%) as a yellow solid, mp >300 °C; IR (Nujol mull): 3509, 1664 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.55 (dd, J = 4.5, 1.7 Hz, 1H), 8.33 (dd, J = 7.6, 1.7 Hz, 1H), 7.55 (s, 1H), 7.31 (dd, J = 7.7, 4.7 Hz, 1H), 5.50 (s, 1H) (NH not observed); ^{13}C NMR (100 MHz, DMSO-d_6): δ 163.7, 152.2, 149.7, 147.5, 142.0, 136.2, 118.9, 113.5, 88.9; MS: *m/z* 186 (M^+). *Anal.* Calcd for $C_9H_6N_4O$: C, 58.06; H, 3.23; N, 30.11. Found: C, 57.94; H, 3.19; N, 30.19.

2-Methylpyrazolo[1,5-*a*]pyrido[3,2-*e*]pyrimidin-5(4*H*)-one (16b). Yield: 71 mg (0.35 mmol, 71%) as a yellow solid, mp >300 °C; IR (Nujol mull): 3071, 1683 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.53 (dd, J = 4.3, 2.2 Hz, 1H), 8.34 (dd, J = 8.0, 2.2 Hz, 1H), 6.76 (dd J = 7.8, 4.2 Hz, 1H), 5.66 (s, 1H), 2.29 (s, 3H) (NH not observed); ^{13}C NMR (100 MHz, DMSO-d_6): δ 158.0, 157.9, 154.2, 153.8, 153.6, 136.3, 112.2, 106.3, 89.4, 15.3; MS: *m/z* 200 (M^+). *Anal.* Calcd for $C_{10}H_8N_4O$: C, 60.00; H, 4.00; N, 28.00. Found: C, 59.93; H, 3.97; N, 28.06.

2-Cyclopropylpyrazolo[1,5-*a*]pyrido[3,2-*e*]pyrimidin-5(4*H*)-one (16c). Yield: 88 mg (0.39 mmol, 78%) as a yellow solid, mp >300 °C; IR (Nujol mull): 3120, 1695 cm^{-1}; ^{1}H NMR (400

MHz, DMSO-d_6): δ 12.6 (s, 1H), 8.72 (d, *J* = 4.4 Hz, 1H), 8.54 (d, *J* = 7.7 Hz, 1H), 7.30 (dd, *J* = 7.8, 4.7 Hz, 1H), 5.82 (s, 1H), 2.04 (m, 1H), 1.00 (m, 2H), 0.85 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 160.9, 154.9, 154.7, 149.8, 142.2, 137.3, 117.5, 107.1, 84.9, 9.7, 8.7; MS: *m/z* 226 (M^+). *Anal*. Calcd for $C_{12}H_{10}N_4O$: C, 63.72; H, 4.42; N, 24.78. Found: C, 63.68; H, 4.39; N, 24.85.

2-(4-Methylphenyl)pyrazolo[1,5-*a*]pyrido[3,2-*e*]pyrimidin-5(4*H*)-one (16d). Yield: 113 mg (0.41 mmol, 82%) as a yellow solid, mp >300 °C; IR (Nujol mull): 3118, 1668 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.57 (dd, *J* = 4.0, 2.3 Hz, 1H), 8.38 (dd, *J* = 8.3, 2.3 Hz, 1H), 7.88 (d, *J* = 7.8 Hz, 2H), 7.26 (d, *J* = 7.8 Hz, 2H), 6.79 (dd, *J* = 7.8, 4.2 Hz, 1H), 6.27 (s, 1H), 2.36 (s, 3H) (NH not observed); ^{13}C NMR (100 MHz, DMSO-d_6) δ 158.0, 157.9, 154.6, 154.4, 154.2, 137.7, 136.4, 132.2, 129.5, 126.4, 112.5, 106.7, 86.8, 21.4; MS: *m/z* 276 (M^+). *Anal.* Calcd for $C_{16}H_{12}N_4O$: C, 69.56; H, 4.35; N, 20.29. Found: C, 69.53; H, 4.34; N, 20.25.

5-Oxo-4,5-dihydropyrazolo[1,5-*a*]pyrido[3,2-*e*]pyrimidine-3-carbonitrile (16f). Yield: 92 mg (0.44 mmol, 87%) as a yellow solid, mp >300 °C; IR (Nujol mull): 3445, 2221, 1673 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.68 (d, *J* = 4.6 Hz, 1H), 8.41 (d, *J* = 7.7 Hz, 1H), 8.02 (s, 1H), 7.47 (dd, *J* = 7.0, 5.4 Hz, 1H) (NH not observed); ^{13}C NMR (100 MHz, DMSO-d_6): δ 165.9, 156.4, 152.0, 147.9, 144.6, 137.7, 121.5, 116.7, 114.5, 74.6; MS: *m/z* 211 (M^+). *Anal.* Calcd for $C_{10}H_5N_5O$: C, 56.87; H, 2.37; N, 33.18. Found: C, 56.89; H, 2.36; N, 33.11.

2.3.3 Benzo[4,5]imidazo[2,1-*b*]quinazolin-12-ones and benzo[4,5]imidazo[1,2-*a*]-pyrido[2,3-*d*]pyrimidin-5-ones

Representative procedure for the synthesis of benzo[4,5]imidazo[2,1-*b*]quinazolin-12-ones and benzo[4,5]imidazo[1,2-*a*]-pyrido[2,3-*d*]pyrimidin-5-ones:

To a stirred reaction mixture of $NaHCO_3$ (2.14 mmol, 2.0 equiv) and benzimidazole (1.28 mmol, 1.2 equiv) in DMF (6 mL) was added dropwise the acid chloride (1.07 mmol, 1.0 equiv) in DMF (4.0 mL) over a period of 30 min at –10 °C. The resulting reaction mass was allowed

to warm to room temperature, maintained for 30 min, and immersed in a preheated oil bath (75-80 °C). The reaction was monitored by TLC (5% MeOH in $CHCl_3$). Upon completion, the DMF was removed under vacuum at 65-70 °C, the residue was made into a slurry in water, and was then filtered. The resulting solid was stirred with ethanol at reflux temperature for 15 min, cooled and filtered.

2-Nitrobenzo[4,5]imidazo[2,1-*b*]quinazolin-12-one (23a): Yield: 88% (264 mg, 0.94 mmol) as a crimson red solid, mp > 300 °C; IR: 3151, 1655, 1548, 1345 cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz): δ 8.95 (d, *J* = 1.7 Hz, 1H), 8.39 (d, *J* = 7.9 Hz, 1H), 8.21 (dd, *J* = 9.3, 1.7 Hz, 1H), 7.49 (d, *J* = 7.9 Hz, 1H), 7.36 (d, *J* = 9.3 Hz, 1H and t, *J* = 7.9 Hz, 1H), 7.12 (t, *J* = 7.7 Hz, 1H) (NH not observed); ^{13}C NMR (DMSO-d_6, 100 MHz, 110 °C): δ 158.8, 149.1, 143.6, 141.4, 133.5 (br), 128.4, 126.8, 126.7, 125.6, (br), 124.3, 122.6, 115.7, 115.3, 113.5 (br); *Anal*. Calcd for $C_{14}H_8N_4O_3$: C, 60.00; H, 2.88; N, 19.99. Found: C, 60.18; H, 2.75; N, 19.79.

2-Fluorobenzo[4,5]imidazo[2,1-*b*]quinazolin-12-one (23b): Yield: 86% (233 mg, 0.92 mmol) as a yellow solid, mp > 300 °C; IR: 3176, 1668 cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz): δ 8.29 (s, 1H), 8.00 (d, *J* = 8.0 Hz, 1H), 7.83 (d, *J* = 8.0 Hz, 1H), 7.52 (t, *J* = 8.0 Hz, 1H), 7.34 (d, *J* = 8.0 Hz, 1H), 7.14 (t, *J* = 8.1 Hz, 2H), 7.01 (t, *J* = 8.0 Hz, 1H) (NH not observed); ^{13}C NMR (DMSO-d_6, 100 MHz, 110 °C): δ 166.5, 158.2 (d, *J* = 241.4 Hz), 157.2, 145.3, 135.0, 130.0, 122.6, 121.7 (d, *J* = 6.1 Hz), 119.1 (d, *J* = 23.2 Hz), 118.5, 116.4 (2C, d, *J* = 7.1 Hz, and s), 113.8 (d, *J* = 23.2 Hz), 111.5; *Anal*. Calcd for $C_{14}H_8FN_3O$: C, 66.40; H, 3.18; N, 16.59. Found: C, 66.47; H, 3.21; N, 16.41.

1-Fluorobenzo[4,5]imidazo[2,1-*b*]quinazolin-12-one (23c): Yield: 93% (252 mg, 1.0 mmol) as a yellow solid, mp > 300 °C; IR: 3160, 1643 cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz): δ 8.41 (d, *J* = 7.9 Hz, 1H), 7.55 (q, *J* = 7.5 Hz, 1H), 7.43 (d, *J* = 7.9 Hz, 1H), 7.35 (t, *J* = 7.6 Hz, 1H), 7.23 (d, *J* = 8.5 Hz, 1H), 7.14 (t, *J* = 7.7 Hz, 1H), 6.88 (dd, *J* = 9.8, 7.2 Hz, 1H) (NH not observed); ^{13}C NMR (DMSO-d_6, 100 MHz, 110 °C): δ 162.4 (d, *J* = 261.6 Hz), 157.7, 152.3,

151.5, 139.7, 133.7 (d, *J* = 12.1 Hz), 128.1, 125.4, 120.2 (d, *J* = 4.0 Hz), 119.5, 115.3, 113.7, 105.7 (d, *J* = 21.2 Hz), 104.3 (d, *J* = 7.1 Hz); *Anal.* Calcd for $C_{14}H_8FN_3O$: C, 66.40; H, 3.18; N, 16.59. Found: C, 66.46; H, 3.16; N, 16.52.

1,2,3,4-Tetrafluorobenzo[4,5]imidazo[2,1-*b*]quinazolin-12-one (23d): Yield: 96% (316 mg, 1.03 mmol) as a yellow solid, mp > 300 °C; IR: 3154, 1651 cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz): δ 8.38 (d, *J* = 8.0 Hz, 1H), 7.42 (d, *J* = 8.0 Hz, 1H), 7.28 (t, *J* = 8.0 Hz, 1H), 7.04 (t, *J* = 8.0 Hz, 1H) (NH not observed); ^{13}C NMR (DMSO-d_6, 100 MHz, 110 °C): δ 163.9, 157.6, 154.9, 146.0 (dm, *J* = 253.5 Hz), 145.3, 142.4 (dm, *J* = 254.5 Hz), 140.4 (dd, *J* = 9.1, 5.1 Hz), 139.7 (dm, *J* = 253.0 Hz), 131.0 (dt, *J* = 239.4, 16.2 Hz), 128.5, 124.8, 117.9, 115.0, 118.0; *Anal.* Calcd for $C_{14}H_5F_4N_3O$: C, 54.74; H, 1.64; N, 13.68. Found: C, 54.82; H, 1.68; N, 13.57.

3-Methylbenzo[4,5]imidazo[2,1-*b*]quinazolin-12-one(23e): Yield: 76% (203 mg, 0.81 mmol) as a white solid, mp > 300 °C; IR: 3159, 1657 cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz): δ 12.5 (br s, 1H), 8.39 (d, *J* = 7.9 Hz, 1H), 8.11 (d, *J* = 8.1 Hz, 1H), 7.45 (d, *J* = 8.0 Hz, 1H), 7.42 (t, *J* = 7.9 Hz, 1H), 7.28 (m, 2H), 7.15 (d, *J* = 8.1 Hz, 1H), 2.45 (s, 3H); ^{13}C NMR (DMSO-d_6, 100 MHz, 110 °C): δ 158.2, 146.7, 144.7 (2C, 1 sharp, 1 br), 136.8 (br), 126.8, 126.1, 125.0, 123.2, 120.4, 119.8 (br), 114.2, 112.8 (br), 111.6, 21.0 ; *Anal.* Calcd for $C_{15}H_{11}N_3O$: C, 72.28; H, 4.45; N, 16.86; Found: C, 72.49; H, 4.48; N, 16.73.

3-Bromobenzo[4,5]imidazo[2,1-*b*]quinazolin-12-one (23f): Yield: 78% (262 mg, 0.84 mmol) as a white solid, mp > 300 °C; IR: 3158, 1662 cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz): δ 12.7 (s, 1H), 8.41 (d, *J* = 8.2 Hz, 1H), 8.14 (d, *J* = 8.2 Hz, 1H), 7.72 (s, 1H), 7.47 (m, 3H), 7.31 (m, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz, 110 °C): δ 158.1, 147.0, 128.0, 127.5, 126.0, 125.3, 124.5, 120.9, 114.5, 113.9 (br), 111.3 (br) (all C not resolvable); *Anal.* Calcd for $C_{14}H_8BrN_3O$: C, 53.53; H, 2.57; N, 13.38; Found: C, 53.59; H, 2.55; N, 13.27.

Benzo[4,5]imidazo[1,2-*a*]pyrido[2,3-*d*]pyrimidin-5-one (23g): Yield: 90% (227 mg, 0.96 mmol) as a yellow solid, mp > 300 °C; IR: 3178, 1644 cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz): δ

8.63 (s, 1H), 8.40 (d, *J* = 7.7 Hz, 1H), 8.35 (d, *J* = 7.8 Hz, 1H), 7.37 (d, *J* = 7.9 Hz, 1H), 7.25 (t, *J* = 7.8 Hz, 1H), 6.99 (t, *J* = 7.9 Hz, 1H), 6.89 (d, *J* = 7.9 Hz, 1H) (NH not observed); ^{13}C NMR (DMSO-d_6, 100 MHz, 110 ^{o}C): δ 161.6, 160.8, 156.1, 152.2, 146.0, 135.9, 128.8, 124.5, 117.2, 115.2, 114.6, 113.3, 107.6; *Anal.* Calcd for $C_{13}H_8N_4O$: C, 66.10; H, 3.41; N, 23.72; Found: C, 66.24; H, 3.46; N, 23.49.

Benzo[4,5]imidazo[2,1-*b*]quinazolin-12-one (23h): Yield: 87% (219 mg, 0.93 mmol) as a white solid, mp > 300 °C; IR: 3170, 1653 cm^{-1}; ^{1}H NMR (DMSO-d_6, 400 MHz): δ 12.69 (br s, 1H), 8.41 (d, *J* = 7.9 Hz, 1H), 8.23 (d, *J* = 8.0 Hz, 1H), 7.92 (t, *J* = 8.0 Hz, 1H), 7.51 (m, 2H), 7.43 (t, *J* = 8.3 Hz, 1H), 7.31 (m, 2H); ^{13}C NMR (DMSO-d_6, 100 MHz, 110 ^{o}C): δ 159.5, 147.5, 145.9 (br), 136.2, (br), 135.1, 127.7, 127.2, 126.2, 122.6, 121.8 (br), 121.5, 115.4, 115.1, 113.5 (br); *Anal.* Calcd for $C_{14}H_9N_3O$: C, 71.48; H, 3.86; N, 17.86. Found: C, 71.37: H, 3.81; N, 17.76.

8,9-Dimethyl-2-nitrobenzo[4,5]imidazo[2,1-*b*]quinazolin-12-one (25a): Yield: 91% (300 mg, 0.97 mmol) as a red solid, mp > 300 °C; IR: 3161, 1647 cm^{-1}; ^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.92 (d, *J* = 1.8 Hz, 1H), 8.17 (s, 1H), 8.11 (dd, *J* = 8.0, 1.8 Hz, 1H), 7.27 (s, 1H), 7.24 (d, *J* = 8.0 Hz, 1H), 2.34 (s, 3H), 2.30 (s, 3H) (NH not observed); ^{13}C NMR (DMSO-d_6, 100 MHz, 110 ^{o}C): δ 160.5, 156.2, 155.2, 143.5, 136.3, 132.9, 127.0 (2C, 1 sharp and 1 br), 125.8 (br), 125.0 (br), 117.0 (br), 115.7 (br), 114.9 (br), 111.6, 20.7 (br), 20.2 (br); *Anal.* Calcd for $C_{16}H_{12}N_4O_3$: C, 62.33; H, 3.92; N, 18.17; Found: C, 62.42; H, 3.96; N, 18.05.

2-Fluoro-8,9-dimethylbenzo[4,5]imidazo[2,1-*b*]quinazolin-12-one (25b): Yield: 87%, (261 mg, 0.93 mmol) as a yellow solid, mp > 300 °C; IR: 3141, 1675 cm^{-1}; ^{1}H NMR (DMSO-d_6, 400 MHz): δ 12.3 (br s, 1H), 8.22 (s, 1H), 7.88 (dd, *J* = 9.1, 2.3 Hz, 1H), 7.66 (td, *J* = 9.0, 2.3 Hz, 1H), 7.57 (dd, *J* = 8.9, 5.0 Hz, 1H), 7.23 (s, 1H), 2.36 (s, 3H), 2.33 (s, 3H); ^{13}C NMR (DMSO-d_6, 100 MHz, 110 ^{o}C): δ 163.1, 157.8, 155.4, 146.7, 146.4, 144.2, 133.7, 128.4, 125.0, 124.1, 121.6, 115.1, 111.4, 109.4, 18.7 (br), 18.4 (br), (the spectrum was not sufficiently resolved to

observe ^{13}C-^{19}F couplings); *Anal*. Calcd for $C_{16}H_{12}FN_3O$: C, 68.32; H, 4.30; N, 14.94. Found: C, 68.59; H, 4.29; N, 14.78.

1-Fluoro-8,9-dimethylbenzo[4,5]imidazo[2,1-*b*]quinazolin-12-one (25c): Yield: 95% (286 mg, 1.01 mmol) as a yellow solid, mp > 300 °C; IR: 3182, 1682 cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz): δ 8.19 (s, 1H), 7.56 (q, *J* = 7.6 Hz, 1H), 7.22 (d, *J* = 7.8 Hz, 1H), 7.21 (s, 1H), 6.81 (dd, *J* = 11.7, 7.9 Hz, 1H), 2.34 (s, 3H), 2.33 (s, 3H), (the NH was not observed); ^{13}C NMR (DMSO-d_6, 100 MHz, 110 °C): δ 162.5 (d, *J* = 260.6 Hz), 157.1, 154.4, 152.1, 150.5, 136.3, 134.0 (br), 133.1, 128.0, 126.2, 120.1 (br), 115.6 (br), 113.8 (br), 106.0 (br), 20.1(br), 19.6 (br) (the spectrum was not sufficiently resolved to observe ^{13}C-^{19}F couplings); *Anal*. Calcd for $C_{16}H_{12}FN_3O$: C, 68.32; H, 4.30; N, 14.94. Found: C, 68.44; H, 4.38; N, 14.89.

1,2,3,4-Tetrafluoro-8,9-dimethylbenzo[4,5]imidazo[2,1-*b*]quinazolin-12-one (25d): Yield: 98% (351 mg, 1.05 mmol) as a yellow solid, mp > 300 °C; IR: 3183, 1667 cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz): δ (ppm) 8.17 (s, 1H), 7.21 (s, 1H), 2.33 (s, 6H), (the NH was not observed); ^{13}C NMR (DMSO-d_6, 100 MHz, 110 °C): δ 161.7, 156.4, 153.6, 145.0 (dm, *J* = 258.6 Hz), 142.7, 141.3 (dm, *J* = 258.6 Hz), 139.3 (dd, *J* = 9.1, 5.1 Hz), 138.5 (dm *J* = 250.5 Hz), 131.7, 129.7 (dt, *J* = 236.3 Hz), 125.8, 124.7, 115.4, 114.6, 19.7, 19.3; *Anal*. Calcd for $C_{16}H_9F_4N_3O$: C, 57.32; H, 2.71; N, 12.53. Found: C, 57.51; H, 2.74; N, 12.51.

3,8,9-Trimethylbenzo[4,5]imidazo[2,1-*b*]quinazolin-12-one (25e): Yield: 80% (237 mg, 0.86 mmol) as a white solid, mp > 300 °C; IR: 3142, 1669 cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz): δ 8.20 (s, 1H), 8.11 (d, *J* = 8.2 Hz, 1H), 7.34 (s, 1H), 7.29 (s, 1H), 7.18 (d, *J* = 8.2 Hz, 1H), 2.46 (s, 3H), 2.37 (s, 3H), 2.33 (s, 3H), (the NH was not observed); ^{13}C NMR (DMSO-d_6, 100 MHz, 110 °C): δ 158.4, 146.4 (br), 142.9 (br), 135.3 (br), 131.4 (br), 131.2, 127.6 (br), 126.8 (br), 125.2, 120.0 (br), 116.2 (br), 115.5 (br), 113.5 (br), 112.9, 21.9 (br), 20.3 (2C, br); *Anal*. Calcd for $C_{17}H_{15}N_3O$: C, 73.63; H, 5.45; N, 15.15. Found: C, 73.57; H, 5.48; N, 15.02.

3-Bromo-8,9-dimethylbenzo[4,5]imidazo[2,1-*b*]quinazolin-12-one (25f): Yield: 84% (307 mg,

0.89 mmol) as a white solid, mp > 300 °C; IR: 3158, 1679 cm^{-1}; ^{1}H NMR (DMSO-d_6, 400 MHz): δ 12.5 (br s, 1H), 8.19 (s, 1H), 8.10 (d, *J* = 8.6 Hz, 1H), 7.69 (s, 1H), 7.42 (d, *J* = 8.5 Hz, 1H), 7.22 (s, 1H), 2.34 (s, 6H); ^{13}C NMR (DMSO-d_6, 100 MHz, 110 °C): δ 158.9, 149.5, 148.2, 134.9, 132.0, 130.0, 129.0 (br), 128.2, 125.3 (2C, 1 sharp and 1 br), 116.5 (br), 115.6 (br), 115.0, 112.9 (br), 20.1, 19.6; *Anal*. Calcd for $C_{16}H_{12}BrN_3O$: C, 56.16; H, 3.53; N, 12.28. Found: C, 56.29; H, 3.53; N, 12.25.

8,9-Dimethylbenzo[4,5]imidazo[1,2-*a*]pyrido[2,3-*d*]pyrimidin-5-one (25g): Yield: 95% (268 mg, 1.0 mmol) as a yellow solid, mp > 300 °C; IR: 3179, 1651 cm^{-1}; ^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.59 (d, *J* = 4.5 Hz, 1H), 8.36 (d, *J* = 7.4 Hz, 1H), 8.14 (s, 1H), 7.17 (s, 1H), 6.84 (dd, *J* = 7.5, 4.5 Hz, 1H), 2.33 (s, 3H), 2.29 (s, 3H), (the NH was not observed); ^{13}C NMR (DMSO-d_6, 100 MHz, 110 °C): δ 161.3, 160.6, 155.6, 155.0, 144.0, 136.0, 132.4, 127.0, 125.1, 116.1, 115.3, 113.1, 107.6, 20.8, 20.4; *Anal*. Calcd for $C_{15}H_{12}N_4O$: C, 68.17; H, 4.58; N, 21.20. Found: C, 68.31; H, 4.45; N, 21.07.

8,9-Dimethylbenzo[4,5]imidazo[2,1-*b*]quinazolin-12-one (25h): Yield: 83% (234 mg, 0.88 mmol) as a white solid, mp > 300 °C; IR: 3142, 1677 cm^{-1}; ^{1}H NMR (DMSO-d_6, 400 MHz): δ 12.4 (br s, 1H), 8.23 (s, 1H and d, *J* = 7.9 Hz, 1H), 7.76 (t, *J* = 7.7 Hz, 1H), 7.51 (d, *J* = 8.2 Hz, 1H), 7.31 (t, *J* = 7.6 Hz, 1H), 7.26 (s, 1H), 2.36 (s, 3H), 2.35 (s, 3H); ^{13}C NMR (DMSO-d_6, 100 MHz, 110 °C): δ 159.3, 147.6, 147.3, 146.9, 134.5, 129.6, 127.4, 126.3, 125.8, 122.4, 122.1, 115.9, 115.5, 113.1, 20.4, 19.4; *Anal*. Calcd for $C_{16}H_{13}N_3O$: C, 72.99; H, 4.98; N, 15.96; Found: C, 73.14; H, 5.04; N, 15.79.

Representative procedure for the *N*-acylation of benzo[4,5]imidazo[2,1-*b*]quinazolin-12-ones:

To a stirred solution of TEA (0.63 mmol) in 5.0 mL of DMSO was added **5** or **7** (0.25 mmol), and the mixture was stirred for 10 min. The acid chloride (0.33 mmol) was added drop-wise to the resulting suspension at 20 °C, and the reaction was stirred for 1 h. Upon completion of the

reaction (monitored by TLC), water (2.0 mL) was added, the mixture was stirred for 10 min and the solid was filtered. The filter cake was washed with water and ether and the product was dried under vacuum at 50 °C for 6-12 h. The *N*-acetyl derivatives were prepared for **23a**, **23b**, **23e**, **25c** and **25h**. For **25b** and **25e**, the acetyl derivatives were still insoluble, and thus the hexanoyl derivatives were prepared.

6-Acetyl-2-nitrobenzo[4,5]imidazo[2,1-*b*]quinazolin-12(6*H*)-one (26a): Yield: 94% (76 mg, 0.235 mmol) as a yellow solid, mp > 300 °C; IR: 1725, 1698, 1603, 1517, 1336 cm^{-1}; ^{1}H NMR (DMSO-d_6, 400 MHz): δ 9.03 (dd, *J* = 2.7, 0.8 Hz, 1H), 8.61-8.57 (complex, 2H), 8.40 (m, 1H), 7.91 (dd, *J* = 9.1, 0.8 Hz, 1H), 7.58 (m, 2H), 3.09 (s, 3H); ^{13}C NMR (DMSO-d_6, 100 MHz, 75 ^{o}C): δ 170.4, 158.9, 158.4, 151.9, 147.6, 144.2, 129.4, 129.0, 128.5, 127.6, 125.9, 123.1, 118.0, 116.2, 115.6, 27.5; *Anal.* Calcd for $C_{16}H_{10}N_4O_4$: C, 59.63; H, 3.13; N, 17.38; Found: C, 59.38; H, 2.98; N, 17.35.

6-Acetyl-1-fluorobenzo[4,5]imidazo[2,1-*b*]quinazolin-12(6*H*)-one (26c): Yield: 96% (71 mg, 0.24 mmol) as a brown solid, mp > 300 °C; IR: 1702, 1685, 1640, 1619, 1376 cm^{-1}; ^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.54 (d, *J* = 7.4 Hz, 1H), 8.38 (d, *J* = 7.6 Hz, 1H), 7.84 (q, *J* = 7.4 Hz, 1H), 7.58-7.47 (m, 3H), 7.26 (t, *J* = 9.6 Hz, 1H), 3.00 (s, 3H); ^{13}C NMR (DMSO-d_6, 100 MHz, 75 ^{o}C): δ 169.5, 160.9 (d, *J* = 263.6 Hz), 155.4, 148.9, 145.2, 134.9 (d, *J* = 11.1 Hz), 128.5, 126.3, 126.2, 124.7, 122.2, 115.3, 114.7, 111.0 (d, *J* = 20.2 Hz), 107.3 (d, *J* = 6.1 Hz), 26.6; *Anal.* Calcd for $C_{16}H_{10}FN_3O_2$: C, 65.08; H, 3.41; N, 14.23. Found: C, 65.23; H, 3.44; N, 14.09.

6-Acetyl-3-methylbenzo[4,5]imidazo[2,1-*b*]quinazolin-12(6*H*)-one (26e): Yield: 92% (67 mg, 0.23 mmol) as a brown solid, mp > 300 °C; IR: 1717, 1694, 1637, 1616, 1374 cm^{-1}; ^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.68 (d, *J* = 8.0 Hz, 1H), 8.49 (d, *J* = 8.0 Hz, 1H), 8.31 (d, *J* = 8.2 Hz, 1H), 7.52 (s, 1H), 7.45 (m, 2H), 7.30 (d, *J* = 8.3 Hz, 1H), 3.12 (s, 3H), 2.54 (s, 3H); ^{13}C NMR (DMSO-d_6, 100 MHz, 75 ^{o}C): δ 170.1, 159.3, 147.4, 145.9, 144.7, 128.8, 127.1, 126.7 (2C), 126.5, 125.3, 116.2, 115.9, 115.7, 27.7, 22.0 (1 aromatic C unresolved); *Anal.* Calcd for

$C_{17}H_{13}N_3O_2$: C, 70.09; H, 4.50; N, 14.42; Found: C, 70.18; H, 4.48; N, 14.34.

2-Fluoro-6-hexanoyl-8,9-dimethylbenzo[4,5]imidazo[2,1-*b*]quinazolin-12(6*H*)-one (27b): Yield: 85% (75 mg, 0.21 mmol) as a white solid, mp 190-191 °C; IR ($CHCl_3$): 1702, 1634, 1385 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 8.43 (s, 1H), 8.29 (s, 1H), 8.03 (dd, *J* = 8.3, 2.4 Hz, 1H), 7.70 (dd, *J* = 8.1, 5.4 Hz, 1H), 7.51 (m, 1H), 3.55 (t, *J* = 7.4 Hz, 2H), 2.40 (s, 3H), 2.39 (s, 3H), 1.88 (quintet, *J* = 7.3 Hz, 2H), 1.57-1.40 (m, 4H), 0.95 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, 25 °C): δ 173.3, 159.8 (d, *J* = 255.8 Hz), 158.6, 144.1 (d, *J* = 22.2 Hz), 136.0, 134.1, 128.8 (d, *J* = 8.1 Hz), 127.1, 124.4, 123.4, 123.1, 119.1 (d, *J* = 8.1 Hz), 117.0, 116.3, 111.5 (d, *J* = 24.2 Hz), 39.0, 31.5, 24.2, 22.6, 20.5, 20.1, 14.0; *Anal.* Calcd for $C_{22}H_{22}FN_3O_2$: C, 69.64; H, 5.84; N, 11.07; Found: C, 69.46; H, 5.52; N, 11.23.

6-Acetyl-1-fluoro-8,9-dimethylbenzo[4,5]imidazo[2,1-*b*]quinazolin-12(6*H*)-one (27c): Yield: 93% (75 mg, 0.232 mmol) as a brown solid, mp > 300 °C; IR: 1707, 1642, 1618, 1377 cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz): δ 8.21 (s, 1H), 8.05 (s, 1H), 7.75 (q, *J* = 7.4 Hz, 1H), 7.43 (d, *J* = 8.2 Hz, 1H), 7.16 (dd, *J* = 11.2, 7.9 Hz, 1H), 2.95 (s, 3H), 2.29 (s, 3H), 2.28 (s, 3H); ^{13}C NMR (DMSO-d_6, 100 MHz, 75 °C): δ 169.2, 16.8 (d, *J* = 264.6 Hz), 155.0, 148.8, 145.0, 134.6 (d, *J* = 10.1 Hz), 134.5, 132.8, 126.4, 124.1, 122.1, 115.8, 115.1, 110.8 (d, *J* = 21.2 Hz), 107.2 (d, *J* = 7.1 Hz), 26.4, 19.5, 19.2; *Anal.* Calcd for $C_{18}H_{14}FN_3O_2$: C, 66.87; H, 4.36; N, 13.00; Found: C, 66.91; H, 4.43; N, 12.86.

6-Hexanoyl-3,8,9-trimethylbenzo[4,5]imidazo[2,1-*b*]quinazolin-12(6*H*)-one (27e): Yield: 97% (91 mg, 0.242 mmol) as a white solid, mp 198-199 °C; IR ($CHCl_3$): 1699, 1634, 1615, 1382 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 8.39 (s, 1H), 8.24 (d, *J* = 8.2 Hz, 1H), 8.23 (s, 1H), 7.44 (s, 1H), 7.23 (d, *J* = 8.2 Hz, 1H), 3.53 (t, *J* = 7.3 Hz, 2H), 2.39 (s, 3H), 2.36 (s, 3H), 2.35 (s, 3H), 1.87 (quintet, *J* = 7.3 Hz, 2H), 1.56-1.40 (m, 4H), 0.97 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, 25 °C): δ 173.4, 159.1, 147.4, 145.6, 144.6, 135.4, 133.8, 127.0, 126.7, 126.6, 126.3, 124.7, 116.9, 116.2, 115.8, 39.0, 31.5, 24.2, 22.6, 22.0, 20.4, 20.1, 14.1; *Anal.* Calcd for $C_{23}H_{25}N_3O_2$: C,

73.57; H, 6.65; N, 11.19; Found: C, 73.41; H, 6.56; N, 11.23.

6-Acetyl-8,9-dimethylbenzo[4,5]imidazo[2,1-*b*]quinazolin-12(6*H*)-one (27h): Yield: 88% (67 mg, 0.22 mmol) as a white solid, mp > 300 °C; IR: 1700, 1638, 1606, 1381 cm^{-1}; ^{1}H NMR (DMSO-d_6, 400 MHz): δ 8.33 (s, 1H), 8.28 (d, *J* = 8.0 Hz, 1H), 8.16 (s, 1H), 7.85 (t, *J* = 7.7 Hz, 1H), 7.69 (d, *J* = 8.1 Hz, 1H), 7.50 (t, *J* = 7.5 Hz, 1H), 3.03 (s, 3H), 2.36 (s, 3H), 2.34 (s, 3H); ^{13}C NMR (DMSO-d_6, 100 MHz, 75 °C): δ 170.1, 158.9, 147.5, 145.4, 135.2, 135.1, 133.6, 127.5, 126.9, 126.7, 125.4, 125.0, 118.3, 116.7, 115.9, 27.3, 20.4, 20.1; *Anal.* Calcd for $C_{18}H_{15}N_3O_2$: C, 70.81; H, 4.95; N, 13.76; Found: C, 70.88; H, 4.93; N, 13.69.

2.3.4 1,3,4-oxadiazoles promoted by NH_4Cl

Representative procedure for the 1,3,4-oxadiazoles synthesis: To a solution of the hydrazide (0.73 mmol) in 10 mL of anhydrous ethanol, added triethyl orthoester (0.81 mmol) and ammonium chloride (0.219 mmol). The solution was stirred and heated to reflux until the reaction was complete (0.5-18 h). The mixture was cooled to room temperature and concentrated under vacuum. The crude product was made into slurry in a mixture of hexanes and ether (3:1), which was filtered and washed with deionized water or purified by column chromatography.

2-Phenyl-1,3,4-oxadiazole (**40a**). Yield: 101 mg (0.69 mmol, 95%) as a colorless liquid. IR: 3140, 1600, 1033 cm^{-1}; ^{1}H NMR (400 MHz): δ 8.47 (s, 1H), 8.11-8.08 (m, 2H), 7.59-7.51 (m, 3H); ^{13}C NMR (100 MHz) δ 164.7, 152.7, 132.0, 129.1, 127.1, 123.5; MS: *m/z* 146 (M^+). *Anal.* Calcd for $C_8H_6N_2O$: C, 65.75; H, 4.14; N, 19.17. Found: C, 65.76; H, 4.18; N, 19.03.

5-Methyl-2-phenyl-1,3,4-oxadiazole (**40b**). Yield: 107 mg (0.67 mmol, 93%) as a white solid, mp 63-64 °C (lit[145] mp 65-67 °C). IR: 3033, 1577, 1070 cm^{-1}; ^{1}H NMR (400 MHz): δ 8.04-8.02 (m, 2H), 7.53-7.47 (m, 3H), 2.62 (s, 3H); ^{13}C NMR (100 MHz) δ 164.87, 163.6, 131.5, 129.0, 126.7, 124.0, 11.1; MS: *m/z* 160 (M^+).

5-Ethyl-2-phenyl-1,3,4-oxadiazole (**40c**). Yield: 125 mg (0.72 mmol, 98%) as a colorless liquid. IR: 3052, 1573, 1070 cm^{-1}; ^{1}H NMR (400 MHz): δ 8.06-8.02 (m, 2H), 7.55-7.47 (m, 3H), 2.96 (q,

J = 7.6 Hz, 2H), 1.45 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (100 MHz) δ 167.8, 164.7, 131.5, 129.0, 126.8, 124.1, 19.2, 10.9; MS: *m/z* 174 (M^+). *Anal.* Calcd for $C_{10}H_{10}N_2O$: C, 68.95; H, 5.79; N, 16.08. Found: C, 68.99; H, 5.77; N, 15.94.

2,5-Diphenyl-1,3,4-oxadiazole (**40d**). Yield: 155 mg (0.70 mmol, 96%) as a tan solid, mp 137-138 °C (lit[146] mp 136-138 °C). IR: 3062, 1548, 1042 cm^{-1}; ^{1}H NMR (400 MHz): δ 8.17-8.14 (m, 4H), 7.58-7.51 (m, 6H); ^{13}C NMR (100 MHz) δ 169.0, 164.6, 131.7, 129.1, 126.9, 123.9; MS: *m/z* 222 (M^+).

2-(p-Tolyl)-1,3,4-oxadiazole (**41a**). Yield: 102 mg (0.64 mmol, 88%) as a white solid, mp 86-87 °C (lit[147] mp 86.9 °C). IR: 3124, 1611, 1070 cm^{-1}; ^{1}H NMR (400 MHz): δ 8.44 (s, 1H), 7.97 (d, *J* = 7.9 Hz, 2H), 7.33 (d, *J* = 7.9 Hz, 2H), 2.44 (s, 3H); ^{13}C NMR (100 MHz) δ 164.9, 152.4, 142.6, 129.8, 127.1, 120.7; MS: *m/z* 160 (M^+).

5-Methyl-2-(p-tolyl)-1,3,4-oxadiazole (**41b**). Yield: 67 mg (0.39 mmol, 53%) as a white solid, mp 96-97 °C. IR: 3015, 1595, 1097 cm^{-1}; ^{1}H NMR (400 MHz): δ 7.91 (d, *J* = 8.2 Hz, 2H), 7.30 (d, *J* = 8.0 Hz, 2H), 2.61 (s, 3H), 2.42 (s, 4H); ^{13}C NMR (100 MHz) δ 165.0, 163.3, 142.0, 129.7, 126.7, 121.2 21.6, 11.1. MS: *m/z* 174 (M^+). *Anal*. Calcd for $C_{10}H_{10}N_2O$: C, 68.95; H, 5.79; N, 16.08. Found: C, 68.91; H, 5.81; N, 15.97.

5-Ethyl-2-(p-tolyl)-1,3,4-oxadiazole (**41c**). Yield: 131 mg (0.69 mmol, 95%) as a colorless liquid. IR: 2991, 1569, 1068 cm^{-1}; ^{1}H NMR (400 MHz): δ 7.92 (d, *J* = 8.2 Hz, 2H), 7.30 (d, *J* = 8.0 Hz, 2H), 2.95 (q, *J* = 7.6 Hz, 2H), 2.42 (s, 3H), 1.44 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (100 MHz) δ 167.5, 164.8, 141.9, 129.7, 126.7, 121.3, 21.6, 19.2, 10.9; MS: *m/z* 188 (M^+). *Anal*. Calcd for $C_{11}H_{12}N_2O$: C, 70.19; H, 6.43; N, 14.88. Found: C, 70.08; H, 6.46; N, 14.72.

5-Phenyl-2-(p-tolyl)-1,3,4-oxadiazole (**41d**). Yield: 165 mg (0.7 mmol, 96%) as a white solid, mp 122-123 °C (lit[146] mp 121-122 °C). IR: 3058, 1616, 1072 cm^{-1}; ^{1}H NMR (400 MHz): δ 8.18-8.10 (m, 2H), 8.05 (d, *J* = 8.2 Hz, 2H), 7.56-7.49 (m, 3H), 7.34 (d, *J* = 7.9 Hz, 2H), 2.45 (s, 3H);

^{13}C NMR (100 MHz) δ 164.7, 164.3, 142.3, 131.6, 129.8, 129.0, 126.9, 124.0, 121.1, 21.7; MS: *m/z* 236 (M^+).

2-(4-Methoxyphenyl)-1,3,4-oxadiazole (**42a**). Yield: 128 mg (0.73 mmol, 100%) as a white solid, mp 61-62 °C (lit[148] mp 63 °C). IR: 3133, 1613, 1095 cm^{-1}; ^{1}H NMR (400 MHz): δ 8.41 (s, 1H), 8.04 (d, *J* = 8.9 Hz, 2H), 7.04 (d, *J* = 8.9 Hz, 2H), 3.89 (s, 3H); ^{13}C NMR (100 MHz) δ 164.7, 162.5, 152.2, 128.9, 116.0, 114.6, 55.5; MS: *m/z* 176 (M^+).

2-(4-Methoxyphenyl)-5-methyl-1,3,4-oxadiazole (**42b**). Yield: 125 mg (0.66 mmol, 90%) as a white solid, mp 84-85 °C. IR: 3045, 1600, 1026 cm^{-1}; ^{1}H NMR (400 MHz): δ 7.98 (d, *J* = 8.9 Hz, 2H), 7.01 (d, *J* = 8.9 Hz, 2H), 3.88 (s, 3H), 2.60 (s, 3H); ^{13}C NMR (100 MHz) δ 164.8, 163.1, 162.2, 128.5, 116.6, 114.4, 55.4, 11.1; MS: *m/z* 190 (M^+). *Anal*. Calcd for $C_{10}H_{10}N_2O_2$: C, 63.15; H, 5.30; N, 14.73. Found: C, 63.22; H, 5.31; N, 14.66.

5-Ethyl-2-(4-methoxyphenyl)-1,3,4-oxadiazole (**42c**). Yield: 139 mg (0.68 mmol, 93%) as a white solid, mp 53-54 °C. IR: 2982, 1614, 1025 cm^{-1}; ^{1}H NMR (400 MHz): δ 7.99 (d, *J* = 8.8 Hz, 2H), 7.01 (d, *J* = 8.8 Hz, 2H), 2.94 (q, *J* = 7.6 Hz, 2H), 1.43 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (100 MHz) δ 167.3, 164.6, 162.1, 128.5, 116.7, 114.4, 55.4, 19.2, 10.9; MS: *m/z* 204 (M^+). *Anal*. Calcd for $C_{11}H_{12}N_2O_2$: C, 64.69; H, 5.92; N, 13.72. Found: C, 64.72; H, 5.94; N, 13.63.

2-(4-Methoxyphenyl)-5-phenyl-1,3,4-oxadiazole (**42d**). Yield: 179 mg (0.71 mmol, 97%) as a white solid, mp 150-151 °C (lit[146] mp 149-150 °C). IR: 3007, 1614, 1017 cm^{-1}; ^{1}H NMR (400 MHz): δ 8.14 – 8.11 (m, 2H), 8.10 (d, *J* = 8.9 Hz, 2H), 7.57-7.50 (m, 3H), 7.07 (d, *J* = 8.8 Hz, 2H), 3.90 (s, 3H); ^{13}C NMR (100 MHz) δ 164.5, 164.1, 162.3, 131.5, 129.0, 128.7, 126.8, 124.1, 116.5, 114.5, 55.5. MS: *m/z* 252 (M^+).

2-(3-Bromophenyl)-1,3,4-oxadiazole (**43a**). Yield: 135 mg (0.6 mmol, 82%) as tan solid, mp 79-80 °C (lit[147] mp 80.1 °C). IR: 2927, 1595, 1066 cm^{-1}; ^{1}H NMR (400 MHz): δ 8.49 (s, 1H), 8.25 (t, *J* = 1.8 Hz, 1H), 8.04 (dt, *J* = 7.8, 1.3 Hz, 1H), 7.70 (ddd, *J* = 8.1, 2.1, 1.1 Hz, 1H), 7.41 (t, *J* = 7.9

Hz, 1H); ^{13}C NMR (100 MHz) δ 163.5, 152.8, 135.0, 130.7, 130.0, 125.7, 125.3, 123.1; MS: *m/z* 224, 226 (M^+).

2-(3-Bromophenyl)-5-methyl-1,3,4-oxadiazole (**43b**). Yield: 155 mg (0.65 mmol, 89%) as a white solid, mp 69-70 °C. IR: 3066, 1572, 1066 cm^{-1}; ^{1}H NMR (400 MHz): δ 8.19 (t, *J* = 1.8 Hz, 1H), 7.99 (dt, *J* = 8.2 Hz, 1.2 Hz, 1H), 7.66 (ddd, *J* = 8.1, 2.0, 1.1 Hz, 1H), 7.38 (t, *J* = 7.9 Hz, 1H), 2.63 (s, 3H); ^{13}C (100 MHz) δ 164.0, 163.6, 134.5, 130.6, 129.6, 125.8, 125.2, 123.1, 11.1; MS: *m/z* 238, 240 (M^+). *Anal*. Calcd for $C_9H_7BrN_2O$: C, 45.22; H, 2.95; N, 11.72. Found: C, 45.34; H, 2.98; N, 11.60.

2-(3-Bromophenyl)-5-ethyl-1,3,4-oxadiazole (**43c**). Yield: 159 mg (0.63 mmol, 86%) as a yellow solid, mp 51-52 °C. IR: 3060, 1571, 1066 cm^{-1}; ^{1}H NMR (400 MHz): δ 8.19 (t, *J* = 1.8 Hz, 1H), 7.99 (ddd, *J* = 7.8, 1.7, 1.0 Hz, 1H), 7.65 (ddd, *J* = 8.1, 2.0, 1.0 Hz, 1H), 7.38 (t, *J* = 7.9 Hz, 1H), 2.97 (q, *J* = 7.6 Hz, 2H), 1.45 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (100 MHz) δ 168.1, 163.4, 134.4, 130.6, 129.6, 125.9, 125.3, 123.0, 19.2, 10.8. MS: *m/z* 252, 254 (M^+). *Anal*. Calcd for $C_{10}H_9BrN_2O$: C, 47.46; H, 3.58; N, 11.07. Found: C, 47.58; H, 3.52; N, 11.12.

2-(3-Bromophenyl)-5-phenyl-1,3,4-oxadiazole (**43d**). Yield: 174 mg (0.58 mmol, 80%), mp 115-116 °C. IR: 3068, 1565, 1058 cm^{-1}; ^{1}H NMR (400 MHz): δ 8.29 (t, *J* = 1.8 Hz, 1H), 8.18-8.13 (m, 2H), 8.10 (dt, *J* = 7.8 Hz, 1H), 7.69 (ddd, *J* = 8.0, 2.0, 1.0 Hz, 1H), 7.61-7.52 (m, 3H), 7.43 (t, *J* = 7.9 Hz, 1H); ^{13}C NMR (100 MHz) δ 164.9, 163.3, 134.7, 132.0, 130.7, 129.7, 129.1, 127.0, 125.8, 125.5, 123.7, 123.1; MS: *m/z* 300,302 (M^+). *Anal*. Calcd for $C_{14}H_9BrN_2O$: C, 55.81; H, 3.01; N, 9.30. Found: C, 55.76; H, 3.08; N, 9.17.

2-(2-Chlorophenyl)-1,3,4-oxadiazole (**44a**). Yield: 36 mg (0.2 mmol, 28%) as a viscous oil. IR: 3125, 1596, 1090 cm^{-1}; ^{1}H NMR (400 MHz): δ 8.56 (s, 1H), 8.01 (dd, *J* = 7.8, 1.7 Hz, 1H), 7.58 (dd, *J* = 8.1, 1.3 Hz, 1H), 7.50 (td, *J* = 7.7, 1.7 Hz, 1H), 7.43 (td, *J* = 7.6, 1.4 Hz, 1H); ^{13}C NMR (100 MHz) δ 163.2, 153.0, 133.3, 132.7, 131.3, 131.3, 127.1, 122.8; MS: *m/z* 180, 182 (M^+). *Anal*. Calcd for $C_8H_5ClN_2O$: C, 53.21; H, 2.79; N, 15.51. Found: C, 53.15; H, 2.86; N, 15.33.

2-(2-Chlorophenyl)-5-phenyl-1,3,4-oxadiazole (**44d**). Yield: 189 mg (0.71 mmol, 97%) as a yellow solid, mp 99-100 °C (lit[149] mp 99-101 °C). IR: 3065, 1590, 1072 cm^{-1}; ^{1}H NMR (400 MHz): δ 8.16 (dd, *J* = 7.5, 2.1 Hz, 2H), 8.12 (dd, *J* = 7.7, 1.9 Hz, 1H), 7.61-7.52 (m, 4H), 7.49 (td, *J* = 7.8, 2.0 Hz, 1H), 7.46 (dt, *J* = 7.6 Hz, 1.3 Hz, 1H); ^{13}C NMR (100 MHz) δ 162.1, 163.1, 133.1, 132.4, 131.9, 131.3, 131.3, 129.1, 127.1, 127.1, 123.8, 123.2; MS: *m/z* 256, 258 (M^{+}).

2-(4-Chlorophenyl)-1,3,4-oxadiazole (**45a**). Yield: 119 mg (0.66 mmol, 90%) as a white solid, mp 134-135 °C. IR: 3099, 1608, 1103 cm^{-1}; ^{1}H NMR (400 MHz): δ 8.48 (s, 1H), 8.03 (d, *J* = 8.6 Hz, 2H), 7.52 (d, *J* = 8.6 Hz, 2H); ^{13}C (100 MHz) δ 164.0, 152.7, 138.4, 129.6, 128.4, 122.0. MS: *m/z* 180, 182 (M^{+}).

2-(4-Chlorophenyl)-5-methyl-1,3,4-oxadiazole (**45b**). Yield: 105 mg (0.54 mmol, 75%) as a yellow solid, mp 107-108 °C. IR: 3076, 1585, 1087 cm^{-1}; ^{1}H NMR (400 MHz): δ 7.97 (d, *J* = 8.6 Hz, 2H), 7.49 (d, *J* = 8.6 Hz, 2H), 2.62 (s, 3H); ^{13}C NMR (100 MHz) δ 164.1, 163.8, 137.8, 129.4, 128.0, 122.5, 11.1; MS: *m/z* 194, 196 (M^{+}).

2-(4-Chlorophenyl)-5-ethyl-1,3,4-oxadiazole (**45c**). Yield: 144 mg (0.69 mmol, 95%) as a white solid, mp 92-94 °C (lit[110] mp 93-94 °C). IR: 3095, 1585, 1083 cm^{-1}; ^{1}H NMR (400 MHz): δ 7.98 (d, *J* = 8.6 Hz, 2H), 7.48 (d, *J* = 8.6 Hz, 2H), 2.96 (q, *J* = 7.6 Hz, 2H), 1.44 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (100 MHz) δ 167.9, 163.9, 137.7, 129.4, 128.0, 122.6, 19.2, 10.8; MS: *m/z* 208, 210 (M^{+}).

2-(4-Chlorophenyl)-5-phenyl-1,3,4-oxadiazole (**45d**). Yield: 130 mg (0.51 mmol, 70%) as a white solid, mp 161-162 °C (lit[110] mp 160-162 °C). IR: 3072, 1552, 1093 cm^{-1}; ^{1}H NMR (400 MHz): δ 8.14 (dd, *J* = 7.7, 1.7 Hz, 2H), 8.09 (d, *J* = 8.6 Hz, 2H), 7.59-7.50 (m, 5H); ^{13}C NMR (100 MHz) δ 164.7, 163.7, 138.0, 131.9, 129.5, 129.1, 128.2, 127.0, 123.7, 122.4; MS: *m/z* 256, 258 (M^{+}).

2-(2-Nitrophenyl)-1,3,4-oxadiazole (**46a**). Yield: 31 mg (0.16 mmol, 22%) as a yellow solid, mp 102-104 °C. IR: 3103, 1560, 1122 cm^{-1}; ^{1}H NMR (400 MHz): δ 8.54 (s, 1H), 8.09 (dd, *J* = 7.2,

2.1 Hz, 1H), 7.99 (dd, *J* = 7.0, 2.1 Hz, 1H), 7.83-7.75 (m, 2H); ^{13}C NMR (100 MHz) δ 161.7, 153.7, 148.2, 133.3, 132.8, 131.9, 124.8, 118.5; MS: *m/z* 191 (M^+). *Anal*. Calcd for $C_8H_5N_3O_3$: C, 50.27; H, 2.64; N, 21.98. Found: C, 50.31; H, 2.68; N, 21.89.

5-Methyl-2-(2-nitrophenyl)-1,3,4-oxadiazole (**46b**). Yield: 37 mg (0.18 mmol, 25%) as a yellow solid, mp 91-92 °C (lit[150] mp 94-95 °C). IR: 3090, 1575, 1108 cm^{-1}; ^{1}H NMR (400 MHz): δ 8.03 (d, *J* = 7.7 Hz, 1H), 7.97 (d, *J* = 7.3 Hz, 1H), 7.75 (quintet, *J* = 7.5 Hz, 2H), 2.61 (s, 3H); ^{13}C NMR (100 MHz) δ 164.9, 161.7, 148.1, 133.1, 132.4, 131.7, 124.7, 118.9, 11.03; MS: *m/z* 205 (M^+). *Anal*. Calcd for $C_9H_7N_3O_3$: C, 52.69; H, 3.44; N, 20.48. Found: C, 52.76; H, 3.45; N, 20.33.

5-Ethyl-2-(2-nitrophenyl)-1,3,4-oxadiazole (**46c**). Yield: 60 mg (0.28 mmol, 38%) as a colorless liquid. IR: 3070, 1570, 1063 cm^{-1}; ^{1}H NMR (400 MHz): δ 8.03 (dd, J = 7.6, 1.7 Hz, 1H), 7.98 (dd, *J*= 7.3, 1.8 Hz, 1H), 7.80-7.70 (m, 2H), 2.95 (q, *J* = 7.6 Hz, 2H), 1.42 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (100 MHz) δ 169.1, 161.5, 148.1, 133.1, 132.3, 131.7, 124.7, 119.0, 19.1, 10.7; MS: *m/z* 219 (M^+). *Anal*. Calcd for $C_{10}H_9N_3O_3$: C, 54.79; H, 4.14; N, 21.90. Found: C, 54.76; H, 4.16; N, 21.78.

2-(2-Nitrophenyl)-5-phenyl-1,3,4-oxadiazole (**46d**). Yield: 107 mg (0.40 mmol, 55%) as a yellow solid, mp 120-121 °C (lit[150] mp 120.5 °C). IR: 3081, 1525, 1064 cm-^{1}; ^{1}H NMR (400 MHz): δ 8.11-8.04 (m, 4H), 7.82-7.74 (m, 2H), 7.59-7.51 (m, 3H); ^{13}C NMR (100 MHz) δ 161.8, 157.3, 144.3, 129.1, 128.6, 128.2, 127.7, 125.2, 123.2, 120.7, 119.4, 114.7; MS: *m/z* 267 (M^+).

2-(4-Nitrophenyl)-1,3,4-oxadiazole (**47a**). Yield: 103 mg (0.54 mmol, 74%) as a yellow solid, mp 154-155 °C (lit[151] mp 156-157 °C). IR: 3106, 1555, 1049 cm^{-1}; ^{1}H NMR (400 MHz): δ 8.57 (s, 1H 8.42 (d, *J* = 8.9 Hz, 2H), 8.32 (d, *J* = 8.9 Hz, 2H); ^{13}C NMR (100 MHz) δ 163.1, 153.4, 149.8, 128.9, 128.1, 124.5; MS: *m/z* 191 (M^+).

5-Methyl-2-(4-nitrophenyl)-1,3,4-oxadiazole (**47b**). Yield: 121.0 mg (0.59 mmol, 81%) as a ellow solid, mp 164-165 °C (lit[144] mp 169-170 °C). IR: 3068, 1581, 1071 cm^{-1}; ^{1}H NMR (400

MHz): δ 8.39 (d, *J* = 8.8 Hz, 2H), 8.24 (d, *J* = 8.8 Hz, 2H), 2.68 (s, 3H); ^{13}C NMR (100 MHz) δ 164.8, 163.2, 149.5, 129.5, 127.6, 124.4, 11.2; MS: *m/z* 205 (M^+).

5-Ethyl-2-(4-nitrophenyl)-1,3,4-oxadiazole (**47c**). Yield: 110mg (0.50 mmol, 69%) as a yellow solid, mp 128-129 °C. IR: 2923, 1566, 1109 cm^{-1}; ^{1}H NMR (400 MHz): δ 8.37 (d, *J* = 8.6 Hz, 2H), 8.24 (d, *J* = 8.7 Hz, 2H), 3.01 (q, *J* = 7.6 Hz, 2H), 1.48 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (100 MHz) δ 168.9, 163.0, 149.5, 129.6, 127.7, 124.3, 19.2, 10.8; MS: *m/z* 219 (M^+). *Anal*. Calcd for $C_{10}H_9N_3O_3$: C, 54.79; H, 4.14; N, 19.17. Found: C, 54.80; H, 4.14; N, 19.13.

2-(4-Nitrophenyl)-5-phenyl-1,3,4-oxadiazole (**47d**). Yield: 126 mg (0.47 mmol, 65%) as a yellow solid, mp 207-208 °C. IR: 3067, 1554, 1095 cm^{-1}; ^{1}H NMR (400 MHz): δ 8.44 (d, *J* = 8.9 Hz, 2H), 8.38 (d, *J* = 8.9 Hz, 2H), 8.20-8.15 (m, 2H), 7.75-7.48 (m, 3H); ^{13}C NMR (100 MHz) δ 165.0, 162.3, 148.9, 131.7, 128.8, 128.7, 127.2, 123.8, 122.7; MS: *m/z* 219 (M^+). *Anal*. Calcd for $C_{14}H_9N_3O_3$: C, 62.92; H, 3.39; N, 15.72. Found: C, 63.01; H, 3.43; N, 15.60.

2.3.5 Nucleophilic addition to polarized vinylarenes

Representative procedure for the addition reaction: To a stirred solution of the nucleophile (active methylene compound or amine, 1.0 mmol) in 10 mL of acetonitrile was added 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU, 0.67 mmol) and the appropriate vinylarene (0.67 mmol). The solution was stirred and heated at reflux until the reaction was complete (4-6 h for malonate, 12-18 h for amines). The reaction mass was cooled to room temperature and concentrated under vacuum. The resulting crude product was purified by column chromatography, eluted with increasing concentrations of ether in hexanes, to give the pure compound. The two isomers of **57b** were separated by silica gel GF preparative TLC (Analtech, No. 02015) using 10% ether in hexanes.

Diethyl 2-(4-nitrophenethyl)malonate (**55a**). Yield: 201 mg (0.65 mmol, 97%) as a colorless oil; IR: 1730, 1519, 1346, 854 cm^{-1}; ^{1}H NMR (400 MHz): δ 8.17 (d, *J* = 8.6 Hz, 2H), 7.38 (d, *J* = 8.5 Hz, 2H), 4.27 (qd, *J* = 4.6, 2.5 Hz, 4H), 3.35 (t, *J* = 7.4 Hz, 1H), 2.80 (t, *J* = 7.4 Hz, 2H), 2.27

(q, *J* = 6.0 Hz, 2H), 1.30 (t, *J* = 7.1 Hz, 6H); ^{13}C NMR (100 MHz): δ 168.9, 148.5, 146.7, 129.3, 123.8, 61.6, 51.1, 33.2, 29.8, 14.1; MS (ESI): *m/z* 310 (M^+ + 1). *Anal.* Calcd for $C_{15}H_{19}NO_6$: C, 58.25; H, 6.19; N, 4.53. Found: C, 58.01; H, 6.31; N, 4.32.

(±)-Diethyl 2-methyl-2-(4-nitrophenethyl)malonate (**55b**). Yield: 201 mg (0.62 mmol, 93%) as a colorless oil; IR: 1729, 1520, 1346, 855 cm^{-1}; ^{1}H NMR (400 MHz): δ 8.17 (d, *J* = 8.6 Hz, 2H), 7.38 (d, *J* = 8.6 Hz, 2H), 4.23 (q, *J* = 7.1 Hz, 4H), 2.73-2.68 (m, 2H), 2.19-2.14 (m, 2H), 1.51 (s, 3H), 1.29 (t, *J* = 7.1 Hz, 6H); ^{13}C NMR (100 MHz): δ 171.9, 149.4, 146.5, 129.2, 123.7, 61.4, 53.5, 37.1, 30.9, 20.1, 14.1; MS (ESI): *m/z* 324 (M^+ + 1). *Anal.* Calcd for $C_{16}H_{21}NO_6$: C, 59.43; H, 6.55; N, 4.33. Found: C, 59.56; H, 6.21; N, 4.22

(±)-Diethyl 2-(2-(4-nitrophenyl)propyl)malonate (**55c**). Yield: 188 mg (0.58 mmol, 87%) as a colorless oil; IR: 1746, 1732, 1524, 1346, 855 cm^{-1}; ^{1}H NMR (400 MHz): δ 8.17 (d, *J* = 8.2 Hz, 2H), 7.34 (d, *J* = 8.2 Hz, 2H), 4.20 (q, *J* = 7.2 Hz, 2H), 4.11 (q, *J* = 7.0 Hz, 2H), 3.13 (t, *J* = 7.8 Hz, 1H), 2.88 (septet, *J* = 7.5 Hz, 1H), 2.28-2.14 (m, 2H), 1.31 (d, *J* = 7.0 Hz, 3H), 1.27 (t, *J* = 7.0 Hz, 3H), 1.22 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (100 MHz): δ 169.1, 169.0, 153.3, 146.8, 128.0, 123.9, 61.6, 50.1, 37.8, 36.5, 22.0, 14.1, 14.0; MS (ESI): *m/z* 324 (M^+ + 1). *Anal.* Calcd for $C_{16}H_{21}NO_6$: C, 59.43; H, 6.55; N, 4.33. Found: C, 59.61; H, 6.38; N, 4.18.

(±)-Diethyl 2-methyl-2-(2-(4-nitrophenyl)propyl)malonate (**55d**). Yield: 192 mg (0.57 mmol, 85%) as a colorless oil; IR: 1729, 1521, 1346, 855 cm^{-1}; ^{1}H NMR (400 MHz): δ 8.14 (d, *J* = 8.1 Hz, 2H), 7.35 (d, *J* = 8.1 Hz, 2H), 4.11 (q, *J* = 7.1 Hz, 2H), 3.96-3.88 (m, 1H), 3.78-3.70 (m, 1H), 3.00-2.91 (m, 1H), 2.40-2.35 (m, 1H), 2.27-2.22 (m, 1H), 1.35 (s, 3H), 1.26 (d, *J* = 6.9 Hz, 6H), 1.22 (t, *J* = 7.4 Hz, 3H), 1.11 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (100 MHz): δ 172.1, 171.7, 154.8, 146.5, 128.2, 123.6, 61.4, 61.1, 53.2, 42.5, 36.3, 24.5, 20.3, 14.0, 13.8; MS: *m/z* 338 (M^+ + 1). *Anal.* Calcd for $C_{17}H_{23}NO_6$: C, 60.52; H, 6.87; N, 4.15. Found: C, 60.27; H, 6.75; N, 3.98.

Diethyl 2-(2-nitrophenethyl)malonate (**55e**). Yield: 195 mg (0.63 mmol, 94%) as a colorless oil; IR: 1730, 1527, 1347 cm^{-1}; ^{1}H NMR (400 MHz): δ 7.93 (d, *J* = 8.0 Hz, 1H), 7.59-7.50 (m,

3H), 7.38 (d, *J* = 7.8 Hz, 2H), 4.33-4.11 (m, 4H), 3.41 (t, *J* = 7.4 Hz, 1H), 3.07-2.82 (m, 3H), 2.40-2.12 (m, 3H), 1.40-1.17 (m, 6H); ^{13}C NMR (100 MHz): δ 169.0, 149.2, 135.9, 133.1, 132.1, 127.5, 124.9, 61.6, 51.6, 30.5, 29.5, 14.1; MS (ESI): *m/z* 310 (M^+ + 1). *Anal*. Calcd for $C_{15}H_{19}NO_6$: C, 58.25; H, 6.19; N, 4.53. Found: C, 58.32; H, 6.05; N, 4.18

(±)-Diethyl 2-methyl-2-(2-nitrophenethyl)malonate (**55f**). Yield: 162 mg (0.5 mmol, 74%) as a colorless oil; IR: 1729, 1527, 1349, 742 cm^{-1}; ^{1}H NMR (400 MHz): δ 7.92 (dd, *J* = 8.0, 1.2 Hz, 2H), 7.55 (td, *J* = 8.0, 1.2 Hz, 2H), 4.25 (q, *J* = 7.1 Hz, 4H), 2.86 (distorted t, *J* = 8.5 Hz, 2H), 2.19 (distorted t, *J* = 8.5 Hz, 2H), 1.53 (s, 3H), 1.29 (t, *J* = 7.1 Hz, 6H); ^{13}C NMR (100 MHz): δ 172.0, 149.2, 136.6, 133.1, 132.2, 127.3, 124.8, 61.4, 53.5, 36.7, 28.3, 19.8, 14.1; MS (ESI): *m/z* 324 (M^+ + 1). *Anal*. Calcd for $C_{16}H_{21}NO_6$: C, 59.43; H, 6.55; N, 4.33. Found: C, 59.13; H, 6.28; N, 4.13.

Diethyl 2-(4-cyanophenethyl)malonate (55h). Yield: 113 mg (0.39 mmol, 58%); as a colorless oil; IR: 2228, 1751, 1731 cm^{-1}; ^{1}H NMR (400 MHz): δ 7.60 (d, *J* = 7.9 Hz, 2H), 7.30 (d, *J* = 7.9 Hz, 2H), 4.23 (m, 4H), 3.35 (t, *J* = 7.4 Hz, 1H), 2.73 (t, *J* = 7.2 Hz, 2H), 2.22 (q, *J* = 7.7 Hz, 2H), 1.28 (t, *J* = 7.1 Hz, 6H); ^{13}C NMR (100 MHz): δ 169.0, 146.3, 132.3, 129.3, 118.9, 110.2, 61.6, 51.1, 33.4, 29.7, 14.1; MS: *m/z* 290 (M^+ + 1). *Anal*. Calcd for $C_{16}H_{19}NO_4$: C, 66.42; H, 6.62; N, 4.84. Found: C: 66.53; H, 6.67; N, 4.61.

(±)-Diethyl 2-(4-cyanophenethyl)-2-methylmalonate (55i). Yield: 109 mg (0.36 mmol, 53%) as a colorless oil; IR: 2228, 1730 cm^{-1}; ^{1}H NMR (400 MHz): δ 7.58 (d, *J* = 8.0 Hz, 2H), 7.30 (d, *J* = 8.0 Hz, 2H), 4.20 (q, *J* = 7.1 Hz, 4H), 2.65 (m, 2H), 2.14 (m, 2H), 1.49 (s, 3H), 1.26 (t, *J* = 7.1 Hz, 6H); ^{13}C NMR (100 MHz): δ 171.9, 147.2, 132.3, 129.2, 119.0, 110.0, 61.4, 53.5, 37.0, 31.1, 20.0, 14.1; MS (ESI): *m/z* 304 (M^+ + 1). *Anal*. Calcd for $C_{17}H_{21}NO_4$: C, 67.31; H, 6.98; N, 4.62. Found: C: 67.41; H, 6.91; N, 4.53.

(±)-Methyl 1-(4-nitrophenethyl)-2-oxocyclopentane-1-carboxylate (**57a**). Yield: 157 mg (0.54 mmol, 81%) as a colorless oil; IR: 1748, 1724, 1518, 1346, 855 cm^{-1}; ^{1}H NMR (400 MHz): δ 8.14

(d, *J* = 8.6 Hz, 2H), 7.34 (d, *J* = 8.6 Hz, 2H), 3.75 (s, 3H), 2.82 (td, *J* = 12.0, 4.9 Hz, 1H), 2.66 (td, *J* = 12.0, 4.9 Hz, 1H), 2.60 (m, 1H), 2.47 (m, 1H), 2.36-2.18 (complex, 2H), 2.12-1.85 (complex, 4H); ^{13}C NMR (100 MHz): δ 214.2, 171.2, 149.2, 146.6, 129.2, 123.7, 60.0, 52.7, 37.9, 35.2, 33.4, 31.2, 19.7; MS (ESI): *m/z* 292 (M^+ + 1). *Anal.* Calcd for $C_{15}H_{17}NO_5$: C, 61.85; H, 5.88; N, 4.81. Found: C, 61.76; H, 5.42; N, 4.70.

Methyl (±)-*R,S*-1-(2-(4-nitrophenyl)propyl)-2-oxocyclopentane-1-carboxylate [**(±)-*R,S*-57b**]. Isomer A; Yield: 79.4 mg (0.26 mmol, 39%) as a colorless oil; IR: 1753, 1722, 1519, 1346, 855 cm^{-1}; ^{1}H NMR (400 MHz): δ 8.15 (d, *J* = 8.1 Hz, 2H), 7.35 (d, *J* = 8.1 Hz, 2H), 3.66 (s, 3H), 3.01 (m, 1H), 2.45 (dd, *J* = 14.4 4.8 Hz, 1H), 2.34 (m, 1H), 2.23 (m, 1H), 2.12 (m, 1H), 1.84 (m, 3H), 1.42 (m, 1H), 1.26 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz): δ 213.8, 170.6, 154.5, 146.6, 128.2, 123.7, 60.6, 52.6, 42.1, 37.2, 33.5, 23.5, 19.5 (1 aliphatic carbon unresolved); MS (ESI): *m/z* 306 (M^+ + 1). *Anal.* Calcd for $C_{16}H_{19}NO_5$: C, 62.94; H, 6.27; N, 4.59. Found: C, 62.68; H, 6.39; N, 4.65.

Methyl (±)-*R,R*-1-(2-(4-nitrophenyl)propyl)-2-oxocyclopentane-1-carboxylate [**(±)-*R,R*-57b**]. Isomer B; Yield: 85.5 mg (0.28 mmol, 43%) as a white solid, mp 51-52 °C; IR: 1752, 1723, 1519, 1346, 855 cm^{-1}; ^{1}H NMR (400 MHz): δ 8.14 (d, *J* = 8.2 Hz, 2H), 7.35 (d, *J* = 8.2 Hz, 2H), 3.33 (s, 3H), 2.94 (m, 1H), 2.67 (m, 1H), 2.54 (dd, *J* = 14.4, 8.7 Hz, 1H), 2.38 (m, 1H), 2.24 (m, 1H), 1.95 (m, 2H), 1.81 (m, 2H), 1.27 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz): δ 213.7, 169.8, 153.9, 146.5, 128.2, 123.6, 60.5, 52.3, 42.0, 37.4, 37.2, 33.0, 23.8, 19.5; MS (ESI): *m/z* 306 (M^+ + 1). *Anal.* Calcd for $C_{16}H_{19}NO_5$: C, 62.94; H, 6.27; N, 4.59. Found: C, 62.75; H, 6.07; N, 4.35.

(±)-Methyl 1-(2-nitrophenethyl)-2-oxocyclopentane-1-carboxylate (**57c**). Yield: 157 mg (0.54 mmol, 80%) as a colorless oil; IR: 1748, 1723, 1525, 1347, 744 cm^{-1}; ^{1}H NMR (400 MHz): δ 7.91 (dd, *J* = 8.2, 1.4 Hz, 1H), 7.53 (td, *J* = 7.6, 1.4 Hz, 1H), 7.40 (dd, *J* = 8.2, 1.4 Hz, 1H), 7.36 (td, *J* = 7.6, 1.4 Hz, 1H), 3.75 (s, 3H), 2.89 (m, 2H), 2.62 (m, 1H), 2.45 (m, 1H), 2.39-2.23 (complex, 2H), 2.13-1.98 (complex, 3H), 1.90 (ddd, *J* = 13.6, 11.8, 5.5 Hz, 1H); ^{13}C NMR (100 MHz): δ

214.4, 171.2, 149.1, 136.5, 133.3, 132.4, 127.4, 124.8, 60.3, 52.7, 37.8, 34.8, 32.7, 28.8, 19.7; MS (ESI): *m/z* 292 (M^+ + 1). *Anal.* Calcd for $C_{15}H_{17}NO_5$: C, 61.85; H, 5.88; N, 4.81. Found: C, 61.48; H, 5.68; N, 4.49.

(±)-Methyl 1-(4-cyanophenethyl)-2-oxocyclopentane-1-carboxylate (57e). Yield: 92 mg (0.34 mmol, 51%); IR: 2228, 1747, 1735 cm^{-1}; ^1H NMR (400 MHz): δ 7.57 (d, *J* = 8.0 Hz, 2H), 7.29 (d, *J* = 8.0 Hz, 2H), 3.72 (s, 3H), 2.76 (td, *J* = 13.1, 5.0 Hz, 1H), 2.60 (m, 2H), 2.47 (m, 1H), 2.36-2.16 (complex, 2H), 2.12-1.80 (complex, 4H); ^{13}C NMR (100 MHz): δ 214.3, 171.2, 147.0, 132.3, 129.2, 119.0, 110.0, 60.1, 52.7, 37.9, 35.2, 33.4, 31.4, 19.7; MS (ESI): *m/z* 272 (M^+ + 1). *Anal*. Calcd for $C_{16}H_{17}NO_3$: C, 70.83; H, 6.32; N, 5.16. Found: C: 70.88; H, 6.30; N, 5.19.

4-(4-Nitrophenethyl)morpholine (**61a**). Yield: 151 mg (0.64 mmol, 95%) as a colorless oil; IR: 1517, 1345, 1116, 858 cm^{-1}; ^1H NMR (400 MHz): δ 8.15 (d, *J* = 8.4 Hz, 2H), 7.37 (d, *J* = 8.4 Hz, 2H), 3.73 (t, *J* = 4.6 Hz, 4H), 2.91 (t, *J* = 7.5 Hz, 2H), 2.64 (t, J = 7.5 Hz, 2H), 2.52 (t, *J* = 4.6 Hz, 4H); ^{13}C NMR (100 MHz): δ 148.2, 146.5, 129.5, 123.7, 123.6, 66.9, 59.8, 53.6, 33.1; MS (ESI): *m/z* 237 (M^+ + 1). *Anal.* Calcd for $C_{12}H_{16}N_2O_3$: C, 61.00; H, 6.83; N, 11.86. Found: C, 60.85; H, 6.74; N, 11.65.

(±)-4-(2-(4-Nitrophenyl)propyl)morpholine (**61b**). Yield: 145 mg (0.58 mmol, 86%) as a colorless oil; IR: 1523, 1345, 1117, 855 cm^{-1}; ^1H NMR (400 MHz): δ 8.14 (d, *J* = 8.4 Hz, 2H), 7.36 (d, *J* = 8.4 Hz, 2H), 3.64 (t, *J* = 4.8 Hz, 4H), 3.07 (sextet, *J* = 7.2 Hz, 1H), 2.48 (m, 2H), 2.42 (t, *J* = 4.8 Hz, 4H), 1.31 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (100 MHz): δ 153.8, 146.5, 128.0, 123.6, 66.9, 65.8, 53.9, 37.3, 19.8; MS (ESI): *m/z* 251 (M^+ + 1). *Anal.* Calcd for $C_{13}H_{18}N_2O_3$: C, 62.38; H, 7.25; N, 11.19. Found: C, 62.28; H, 7.05; N, 11.31.

4-(2-Nitrophenethyl)morpholine (**61c**). Yield: 134 mg (0.57 mmol, 85%) as a colorless oil; IR: 1524, 1353, 1116, 742 cm^{-1}; ^1H NMR (400 MHz): δ 7.90 (dd, *J* = 8.2, 0.9 Hz, 1H), 7.51 (td, *J* = 7.4, 0.9 Hz, 1H), 7.37 (d, *J* = 8.2 Hz, 1H), 7.35 (obscured td, *J* ≈ 7.4, 1.0 Hz, 1H), 3.72 (t, *J* = 4.6 Hz, 4H), 3.10 (distorted t, *J* = 8.0 Hz, 2H), 2.64 (distorted t, *J* = 8.0 Hz, 2H), 2.53 (t, *J* = 4.6 Hz,

4H); ^{13}C NMR (100 MHz): δ 149.7, 135.3, 132.9, 132.4, 127.3, 124.7, 67.0, 59.5, 53.6, 30.3; MS (ESI): *m/z* 237 (M^+ + 1). *Anal.* Calcd for $C_{12}H_{16}N_2O_3$: C, 61.00; H, 6.83; N, 11.86. Found: C, 61.12; H, 6.75; N, 11.92.

1-(4-Nitrophenethyl)piperidine (**62a**). Yield: 146 mg (0.62 mmol, 93%) as a colorless oil; IR: 1524, 1353, 1116, 742 cm^{-1}; ^{1}H NMR (400 MHz): δ 8.14 (d, *J* = 8.4 Hz, 2H), 7.36 (d, *J* = 8.4 Hz, 2H), 2.91 (distorted t, *J* = 7.5 Hz, 2H), 2.58 (distorted t, *J* = 7.5 Hz, 2H), 2.46 (t, *J* = 5.2 Hz, 4H), 1.61 (quintet, *J* = 5.7 Hz, 4H), 1.46 (quintet, *J* = 5.9 Hz, 2H); ^{13}C NMR (100 MHz): δ 148.8, 146.4, 129.5, 123.6, 60.4, 54.5, 33.6, 26.0, 24.4; MS (ESI): *m/z* 235 (M^+ + 1). *Anal.* Calcd for $C_{13}H_{18}N_2O_2$: C, 66.64; H, 7.74; N, 11.96. Found: C, 66.51; H, 7.52; N, 11.69.

(±)-1-(2-(4-Nitrophenyl)propyl)piperidine (**62b**). Yield: 140 mg (0.56 mmol, 84%) as a colorless oil; IR: 1519, 856 cm^{-1}; ^{1}H NMR (400 MHz): δ 8.15 (d, *J* = 8.1 Hz, 2H), 7.36 (d, *J* = 8.1 Hz, 2H), 3.07 (sextet, *J* = 7.2 Hz, 1H), 2.43 (d, *J* = 7.4 Hz, 2H), 2.35-2.32 (m, 4H), 1.53-1.47 (m, 4H), 1.41-1.37 (m, 2H), 1.27 (d, *J* = 7.5 Hz, 3H); ^{13}C NMR (100 MHz): δ 154.5, 146.4, 128.1, 123.5, 66.3, 55.0, 37.7, 26.0, 24.4, 19.9; MS (ESI): *m/z* 249 (M^+ + 1). *Anal.* Calcd for $C_{14}H_{20}N_2O_2$: C, 67.72; H, 8.12; N, 11.28. Found: C, 68.13; H, 8.02; N, 11.70.

1-(2-Nitrophenethyl)piperidine (**62c**). Yield: 138 mg (0.59 mmol, 88%) as a colorless oil; IR: 1525, 1350, 860 cm^{-1}; ^{1}H NMR (400 MHz): δ 7.89 (dd, *J* = 8.1, 0.9 Hz, 1H), 7.51 (td, *J* = 7.5, 1.0 Hz, 1H), 7.38 (dd, *J* = 8.1, 0.9 Hz, 1H), 7.34 (td, *J* = 7.5, 1.0 Hz, 1H), 3.11 (distorted t, *J* = 7.7 Hz, 2H), 2.62 (distorted t, *J* = 7.7 Hz, 2H), 2.49 (m, 4H), 1.60 (quintet, *J* = 5.6 Hz, 4H), 1.44 (quintet, *J* = 5.8 Hz, 2H); ^{13}C NMR (100 MHz): δ 149.6, 135.7, 132.9, 132.5, 127.1, 124.6, 59.9, 54.4, 30.4, 26.0, 24.4; MS (ESI): *m/z* 235 (M^+ + 1). *Anal.* Calcd for $C_{13}H_{18}N_2O_2$: C, 66.64; H, 7.74; N, 11.96. Found: C, 66.51; H, 7.79; N, 11.83.

***N*-Benzyl-2-(4-nitrophenyl)ethan-1-amine** (**63a**). Yield: 141 mg (0.55 mmol, 82%) as a red oil; IR: 3310, 1516, 1345, 855 cm^{-1}; ^{1}H NMR (400 MHz): δ 8.15 (d, *J* = 8.5 Hz, 2H), 7.36 (d, *J* = 8.5 Hz, 2H), 7.36-7.25 (complex, 5H), 3.81 (s, 2H), 2.93 (t, *J* = 3.8 Hz, 4H), 1.68 (br s, 1H); ^{13}C

NMR (100 MHz): δ 148.0, 146.6, 139.8, 129.5, 128.5, 128.1, 127.1, 123.7, 53.8, 49.8, 36.3; MS (ESI): *m/z* 255 (M^+ + 1). *Anal.* Calcd for $C_{15}H_{16}N_2O_2$: C, 70.29; H, 6.29; N, 10.93. Found: C, 70.15; H, 6.70; N, 11.08.

(±)-*N*-Benzyl-2-(4-nitrophenyl)propan-1-amine (**63b**). Yield: 139 mg (0.52 mmol, 77%) as a yellow oil; IR: 3356, 1516, 1344, 854 cm^{-1}; ^1H NMR (400 MHz): δ 8.16 (d, *J* = 8.4 Hz, 2H), 7.35 (d, *J* = 8.4 Hz, 2H), 7.32-7.28 (m, 2H), 7.26-7.22 (m, 3H), 3.76 (d, *J* = 4.21 Hz, 2H), 3.06 (septet, *J* = 7.0 Hz, 1H), 2.82 (d, *J* = 7.1 Hz, 2H), 1.43 (br s, 1H), 1.28 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (100 MHz): δ 153.4, 146.6, 140.1, 128.4, 128.1, 128.0, 127.0, 123.8, 55.8, 53.8, 40.4, 19.7; MS (ESI): *m/z* 271 (M^+ + 1). *Anal.* Calcd for $C_{16}H_{18}N_2O_2$: C, 71.09; H, 6.71; N, 10.36. Found: C, 71.38; H, 6.58; N, 10.47.

***N*-Benzyl-2-(2-nitrophenyl)ethan-1-amine** (**63c**). Yield: 134 mg (0.52 mmol, 78%) as a brown oil; IR: 3346, 1524, 1347, 740 cm^{-1}; ^1H NMR (400 MHz): δ 7.90 (d, *J* = 8.1 Hz, 1H), 7.51 (t, *J* = 8.0 Hz, 1H), 7.36 (apparent d, *J* = 8.1 Hz, 1H), 7.36-7.20 (complex, 6H), 3.82 (s, 2H), 3.11 (t, *J* = 7.4 Hz, 2H), 2.94 (t, *J* = 7.3 Hz, 2H), 1.50 (br s, 1H); ^{13}C NMR (100 MHz): δ 149.6, 140.2, 135.2, 132.9, 132.3, 128.4, 128.1, 127.3, 127.0, 124.8, 53.7, 49.7, 33.6; MS (ESI): *m/z* 257 (M^+ + 1). *Anal.* Calcd for $C_{15}H_{16}N_2O_2$: C, 70.29; H, 6.29; N, 10.93. Found: C, 70.18; H, 6.42; N, 10.79.

2.3.6 Bismuth triflate catalyzed synthesis of 4-chromanone

Representative procedure for the preparation of aryl 3,3-dimethylacrylates (68). The general procedure of Dawson and co-workers was followed.[33] To an oil free suspension of sodium hydride (0.60 g, 25.0 mmol) in 10 mL of anhydrous THF, a solution of the phenol (23.1 mmol) in 30 mL of THF was added over a 5-min period with stirring at 0 °C (ice bath). The solution was stirred for 10 min and treated with a solution of 3-methyl-2-butenoyl chloride (2.78 g, 23.3 mmol) in 15 mL of dry THF over a 5-min period at 0 °C. The reaction was then allowed to warm to room temperature over a 3-h period. The white suspension was transferred to separatory funnel containing water (75 mL) and acetic acid (0.5 mL) and was gently shaken. The mixture was

extracted with ether (2 × 50 mL) and the extract was washed with saturated aq NaCl (3 × 50 mL), dried ($MgSO_4$), and concentrated to give a light yellow oil. The product was purified on a 40-cm × 2.5-cm silica gel column eluted with 10% ether in hexanes to give the pure ester.

Phenyl 3-methyl-2-butenoate (68a). Yield: 3.61 g (20.6 mmol, 89%) as a colorless oil. IR: 1738, 1653 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.38 (t, *J* = 7.9 Hz, 2H), 7.20 (t, *J* = 7.8 Hz, 1H), 7.10 (d, *J* = 8.0 Hz, 2H), 5.91 (m, 1H), 2.22 (d, *J* = 1.8 Hz, 3H), 1.96 (d, *J* = 1.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.9, 159.9, 150.7, 129.3, 125.5, 121.8, 115.3, 27.6, 20.5; HRMS (ESI) *m/z* Calcd for $[C_{11}H_{12}O_2 + H]^+$: 177.0916; found: 177.0910.

4-Methylphenyl 3-methyl-2-butenoate (68b): Yield**:** 4.30 g (22.6 mmol, 98%) as a colorless oil; IR: 1738, 1650 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.16 (d, *J* = 8.0 Hz, 2H), 6.97 (d, *J* = 8.0 Hz, 2H), 5.90 (s, 1H), 2.33 (s, 3H), 2.22 (s, 3H), 1.97 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.1, 159.6, 148.4, 135.1, 129.8, 121.5, 115.3, 27.6, 20.9, 20.5; HRMS (ESI) *m/z* Calcd for $[C_{12}H_{14}O_2 + H]^+$: 191.1072; found: 191.1073.

3-Methylphenyl 3-methyl-2-butenoate (68c). Yield: 4.25 g (22.4 mmol, 97%) as a colorless oil; IR: 1739, 1647 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.24 (t, *J* = 7.7 Hz, 1H), 7.02 (d, *J* = 7.7 Hz, 1H), 6.91 (s, 1H), 6.89 (d, *J* = 7.7 Hz, 1H), 5.90 (s, 1H), 2.35 (s, 3H), 2.23 (s, 3H), 1.97 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.1, 159.7, 150.6, 139.5, 129.1, 126.3, 122.4, 118.8, 115.3, 27.7, 21.3, 20.5; HRMS (ESI) *m/z* Calcd for $[C_{12}H_{14}O_2 + H]^+$: 191.1072; found: 191.1062.

3,5-Dimethylphenyl 3-methyl-2-butenoate (68d): Yield: 4.23 g (20.7 mmol, 89%) as a colorless oil; IR: 1734, 1650 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 6.84 (s, 1H), 6.97 (s, 2H), 5.89 (s, 1H), 2.30 (s, 6H), 2.22 (s, 3H), 1.97 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.2, 159.5, 150.6, 139.1, 127.3, 119.4, 115.3, 27.6, 21.2, 20.4; HRMS (ESI) *m/z* Calcd for $[C_{13}H_{16}O_2 + H]^+$: 205.1229; found: 205.1222.

2-Isopropyl-5-methylphenyl 3-methyl-2-butenoate (68e): Yield: 5.19 g (22.3 mmol, 96%) as a colorless oil; IR: 1738, 1650 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.19 (d, *J* = 7.9 Hz, 1H), 7.00

(d, J = 7.9 Hz, 1H), 6.83 (s, 1H), 5.95 (apparent sextet, J = 1.3 Hz, 1H), 2.99 (d septet, J = 6.8, 1.3 Hz, 1H), 2.32 (s, 3H), 2.23 (s, 3H), 1.99 (s, 3H), 1.19 (dd, J = 8.0, 1.9 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.2, 159.5, 147.8, 137.2, 136.4, 126.8, 126.3, 123.0, 115.2, 27.6, 27.1, 23.1, 20.8, 20.5; HRMS (ESI) *m/z* Calcd for $[C_{15}H_{20}O_2 + H]^+$: 233.1542; found: 233.1548.

3-Fluorophenyl 3-methyl-2-butenoate (68f): Yield: 4.07 g (21.0 mmol, 90%) as a colorless oil; IR: 1739, 1648, 1123 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34 (AB pattern, J = 7.8 Hz, 1H), 6.95-6.84 (complex, 3H), 5.89 (s, 1H), 2.23 (s, 3H), 1.99 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.4, 162.9 (d, J = 247.0 Hz), 160.8, 151.6 (d, J = 10.8 Hz), 130.0 (d, J = 9.5 Hz), 117.6 (d, J = 3.3 Hz), 114.8, 112.5 (d, J = 21.0 Hz), 109.9 (d, J = 24.1 Hz), 27.7, 20.6; HRMS (ESI) *m/z* Calcd for $[C_{11}H_{11}FO_2 + H]^+$: 195.0821; found: 195.0825.

3-Methoxyphenyl 3-methyl-2-butenoate (68g): Yield: 4.61 g (22.4 mmol, 96%) as a colorless oil; IR: 2838, 1740, 1648 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.26 (t, J = 8.2 Hz, 1H), 6.77 (ddd, J = 8.2, 2.3, 0.7 Hz, 1H), 6.70 (ddd, J = 8.0, 2.3, 0.7 Hz, 1H), 6.66 (t, J = 2.3 Hz, 1H), 5.91 (s, 1H), 3.79 (s, 3H), 2.23 (s, 3H), 1.98 (s, 3H); ^{13}C NMR 100 MHz, $CDCl_3$): δ 164.8, 160.4, 160.0, 151.7, 129.7, 115.2, 114.1, 111.4, 107.7, 55.4, 27.6, 20.5; HRMS (ESI) *m/z* Calcd for $[C_{12}H_{14}O_3 + H]^+$: 207.1021; found: 207.1017.

Reaction of 3-methylphenyl 3-methyl-2-butenoate (68c) with aluminum chloride. A 250-mL three-necked round-bottomed flask equipped with a stir bar, an addition funnel and a condenser (with a drying tube) was charged with dichloromethane (40 mL) and $AlCl_3$ (1.19 g, 8.95 mmol). The resulting suspension was stirred and cooled to 0 °C (ice bath), and a solution of **68c** (1.00 g, 5.26 mmol) in dichloromethane (10 mL) was added dropwise. The reaction was gradually warmed to room temperature and stirring was continued for 65 h. The resulting brown solution was added to a mixture of ice and saturated aq NaCl, the layers were separated, and the aqueous layer was extracted with dichloromethane (40 mL). The combined organic extracts were washed with saturated aq NaCl (2 × 50 mL), dried ($MgSO_4$), and concentrated to give a brown

oil, which was purified on a 30 cm × 2.5 cm silica gel column eluted with increasing concentrations (2-10%) of ether in hexanes to give four bands: band 1 (highest R_f), 1-(2-hydroxy-4-methylphenyl)-3-methyl-2-buten-1-one (**70c**, 181 mg, 0.95 mmol, 18%) as a yellow oil; band 2, 3-methylphenyl 3-methyl-2-butenoate (**68c**, 51 mg, 0.26 mmol, 5%); band 3, 2,2,7-trimethyl-4-chromanone (**71c**, 648 mg, 3.41 mmol, 65%) as a white solid, mp 69-70 °C; and band 4, 4,4,7-trimethyl-2-chromanone (**69c**, 21 mg, 0.011 mmol, 2%) as a yellow oil. The spectral data were as follows:

Band 1 (**70c**): IR: 3200-2700 (broad), 1640, 1583 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 12.9 (s, 1H), 7.65 (d, *J* = 8.0 Hz, 1H), 6.78 (s, 1H), 6.74 (s, 1H), 6.68 (d, *J* = 8.0 Hz, 1H), 2.34 (s, 3H), 2.20 (s, 3H), 2.03 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 195.8, 163.4, 157.1, 147.3, 126.8, 120.1, 119.8, 118.5, 118.4, 28.2, 21.9, 21.3; HRMS (ESI) *m/z* Calcd for $[C_{12}H_{14}O_2 + H]^+$: 191.1072; found: 191.1065.

Band 2 (**68c**, recovered starting material): The spectral data matched those reported for **68c** above.

Band 3 (**71c**): The spectral data matched those reported for **71c** below.

Band 4 (**69c**): IR: 1772, 1625, 1581 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.19 (d, *J* = 7.8 Hz, 1H), 6.96 (dd, *J* = 7.8, 1.7 Hz, 1H), 6.87 (d, *J* = 1.7 Hz, 1H), 2.60 (s, 2H), 2.33 (s, 3H), 1.33 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.5, 150.5, 138.5, 128.7, 125.5, 124.2, 117.5, 43.8, 33.0, 27.8, 21.0; HRMS (ESI) *m/z* Calcd for $[C_{12}H_{14}O_2 + H]^+$: 191.1072; found: 191.1069.

General procedure for the preparation of 4-chromanones from aryl 3,3-dimethylacrylates. A solution of the aryl 3,3-dimethylacrylate (**68**, 1.00 mmol) and bismuth(III) triflate (131 mg, 20 mol%) in 8 mL of toluene was boiled for 12-24 h and monitored by TLC. Each reaction was worked up by cooling, removing the solvent, diluting with 1 mL of chloroform, and applying the crude product mixture directly to a 20 cm × 20 cm PTLC plate. After the chloroform had been dried, the plate was eluted with 5% ether in hexanes (8-10% ether in hexanes for the methoxy-

substituted products) to give three major bands. The bright blue fluorescent band (the 4-chromanone) was accompanied by small amounts of the starting ester (a faster moving band) and the corresponding phenol (a slower moving band). For 2-isopropyl-5-methylphenol, the 4-chromanone (40%) was accompanied by larger quantities of aryl 3,3-dimethylacrylate (12%) and phenol (30%). The spectra for all of the 4-chromanones and some of the aryl esters isolated are listed below.

Conversion of Fries product 70c to 4-chromanone 71c. A toluene solution of 1-(2-hydroxy-4-methylphenyl)-3-methyl-2-buten-1-one (**70c**, 60 mg, 0.31 mmol) and bismuth(III) triflate (41 mg, 0.06 mmol, 20 mol%) was heated at reflux for 15 min. The solvent was removed under vacuum and the remaining oil was filtered through a short plug of silica gel using 5% ether in hexanes. Removal of the solvent under vacuum afforded 2,2,7-trimethyl-4-chromanone (**71c**, 57 mg, 0.30 mmol, 95%). The spectral data matched those reported for **71c** below.

General procedure for the preparation of 4-chromanones from the phenol and the carboxylic acids. To a solution of the phenol (**72**, 1.0 mmol) and the dimethylacrylic acid or crotonic acid (1.0 mmol) in 8 mL of toluene was added bismuth(III) triflate (41 mg, 0.06 mmol, 20 mol%). The reaction was heated under reflux for 12-24 h and then cooled. Removal of the solvent under vacuum and purification by PTLC eluted with 5% ether in hexane (8-10% ether in hexanes for the methoxy-substituted products) showed several bands. The major band (bright fluorescent blue) was isolated and extracted with ether to give the 4-chromanone **71** or **73**. The other bands consisted of varying amounts of the aryl ester of the carboxylic acid and unreacted phenol. The following compounds were prepared by this method.

2,2,6-Trimethyl-4-chromanone (**71b**): Yield: 140 mg (0.74 mmol, 74%) as a colorless oil (lit[152] reports a mp of 67 ^{o}C); IR: 1692, 1619 cm^{-1}; ^{1}H NMR: δ 7.65 (s, 1H), 7.28 (d, J = 8.4 Hz, 1H), 6.83 (d, J = 8.4 Hz, 1H), 2.69 (s, 2H), 2.34 (s, 3H), 1.45 (s, 6H); ^{13}C NMR: δ 192.8, 158.0, 137.2,

130.0, 126.1, 119.8, 118.1, 79.0, 48.9, 26.6, 20.4; HRMS (ESI) *m/z* Calcd for $[C_{12}H_{14}O_2 + H]^+$: 191.1072; found: 191.1077.

2,2,7-Trimethyl-4-chromanone (**71c**): Yield: 129 mg (0.68 mmol, 68%) as a white solid, mp 69-70 °C (lit[153] mp 70 °C); IR: 1686, 1617 cm^{-1}; ^1H NMR: δ 7.75 (d, *J* = 8.0 Hz, 1H), 6.79 (d, *J* = 8.0 Hz, 1H), 6.73 (s, 1H), 2.69 (s, 2H), 2.30 (s, 3H), 1.44 (s, 6H); ^{13}C NMR: δ 192.2, 160.0, 149.6, 126.4, 122.0, 118.3, 118.0, 79.1, 48.8, 26.7, 21.9; HRMS (ESI) *m/z* Calcd for $[C_{12}H_{14}O_2 + H]^+$: 191.1072; found: 191.1074.

2,2,5,7-Tetramethyl-4-chromanone (**71d**): Yield: 140 mg (0.69 mmol, 69%) as a white solid, mp 61-63 °C; IR: 1682, 1614 cm^{-1}; ^1H NMR: δ 6.60 (s, 1H), 6.57 (s, 1H), 2.67 (s, 2H), 2.59 (s, 3H), 2.28 (s, 3H), 1.43 (s, 6H); ^{13}C NMR: δ 194.1, 161.5, 146.3, 141.8, 125.6, 116.9, 116.8, 78.4, 50.8, 27.0, 23.1, 22.1; HRMS (ESI) *m/z* Calcd for $[C_{13}H_{16}O_2 + H]^+$: 205.1229; found: 205.1223.

2,2,5-Trimethyl-8-isopropyl-4-chromanone (**71e**): Yield: 102 mg (0.44 mmol, 44%; 54% brsm—based on recovered phenol) as a white solid, mp 73-75 °C; IR: 1684, 1578 cm^{-1}; ^1H NMR: δ 7.23 (d, *J* = 7.7 Hz, 1H), 6.71 (d, *J* = 7.7 Hz, 1H), 3.25 (septet, *J* = 6.9 Hz, 1H), 2.70 (s, 2H), 2.59 (s, 3H), 1.45 (s, 6H), 1.21 (d, *J* = 6.9 Hz, 6H); ^{13}C NMR: δ 194.6, 158.1, 138.5, 135.3, 131.3, 123.4, 118.6, 77.8, 50.3, 26.9, 26.6, 22.7, 22.4; HRMS (ESI) *m/z* Calcd for $[C_{15}H_{20}O_2 + H]^+$: 233.1542; found: 233.1541. A faster moving band contained 2-isopropyl-5-methylphenyl 3-methyl-2-butenoate [**68e** (X= 2-*i*-Pr-5-Me), 51 mg, 0.22 mmol, 22%; 27% brsm] as a colorless oil. The spectral data matched those reported above.

7-Fluoro-2,2-dimethyl-4-chromanone (**71f**): Yield: 126 mg (0.65 mmol, 65%) as a colorless oil; IR: 1694, 1616 cm^{-1}; ^1H NMR: δ 7.78 (dd, *J* = 8.8, 6.8 Hz, 1H), 6.69 (td, *J* = 8.5, 2.4 Hz, 1H), 6.62 (dd, *J* = 10.1, 2.4 Hz, 1H), 2.71 (s, 2H), 1.46 (s, 6H); ^{13}C NMR: δ 191.1, 167.8 (d, *J* = 238.4 Hz), 161.7 (d, *J* = 13.6 Hz), 129.0 (d, *J* = 11.4 Hz), 117.8 (d, *J* = 2.5 Hz), 109.7 (d, *J* = 22.7 Hz), 105.7 (d, *J* = 24.3 Hz), 80.1, 48.6, 26.6; HRMS (ESI) *m/z* Calcd for $[C_{11}H_{11}FO_2 + H]^+$: 195.0821; found: 195.0815.

7-Methoxy-2,2-dimethyl-4-chromanone (**71g**): Yield: 93 mg (0.45 mmol, 45%) as a colorless solid, mp 79-81 °C (lit[154] mp 81-82 °C); IR: 2838, 1681, 1609 cm^{-1}; ^1H NMR: δ 7.79 (d, *J* = 8.8 Hz, 1H), 6.55 (dd, *J* = 8.8, 2.4 Hz, 1H), 6.38 (d, *J* = 2.4 Hz, 1H), 3.83 (s, 3H), 2.67 (s, 2H), 1.46 (s, 6H); ^{13}C NMR: δ 191.1, 166.2, 162.0, 128.3, 114.1, 109.3, 101.1, 79.6, 55.4, 48.6, 26.7; HRMS (ESI) *m/z* Calcd for $[C_{12}H_{14}O_3 + H]^+$: 207.1021; found: 207.1012.

2,2,5,8-Tetramethyl-4-chromanone (**71h**): Yield: 51 mg (0.25 mmol, 25%; 42% brsm) as a colorless oil; IR: 1688, 1586 cm^{-1}; ^1H NMR: δ 7.16 (d, *J* = 7.5 Hz, 1H), 6.64 (d, *J* = 7.5 Hz, 1H), 2.69 (s, 2H), 2.58 (s, 3H), 2.17 (s, 3H), 1.44 (s, 6H); ^{13}C NMR: δ 193.5, 159.0, 138.7, 135.5, 125.0, 123.0, 118.4, 77.9, 50.3, 26.7, 22.6, 16.0; HRMS (ESI) *m/z* Calcd for $[C_{13}H_{16}O_2 + H]^+$: 205.1229; found: 205.1225. A faster moving band contained 2,5-dimethylphenyl 3-methyl-2-butenoate [**68h** (X = 2,5-diMe), 45 mg, 0.22 mmol, 22%; 37% brsm] as a colorless oil. IR: 1734, 1649 cm^{-1}; ^1H NMR: δ 7.10 (d, *J* = 7.7 Hz, 1H), 6.94 (d, *J* = 7.7 Hz, 1H), 6.83 (s, 1H), 5.94 (apparent t, *J* = 0.7 Hz, 1H), 2.31 (s, 3H), 2.23 (d, *J* = 0.7 Hz, 3H), 2.13 (s, 3H), 1.99 (d, *J* = 0.7 Hz, 3H); ^{13}C NMR: δ 164.8, 159.6, 149.1, 136.7, 130.7, 127.0, 126.5, 122.6, 115.1, 27.6, 20.9, 20.5, 15.8; HRMS (ESI) *m/z* Calcd for $[C_{13}H_{16}O_2 + H]^+$: 205.1229; found: 205.1221.

2,2,6,7-Tetramethyl-4-chromanone (**71i**): Yield: 178 mg (0.87 mmol, 87%) as a white solid, mp 69-71 °C; IR: 1688, 1621 cm^{-1}; ^1H NMR: δ 7.59 (s, 1H), 6.72 (s, 1H), 2.67 (s, 2H), 2.25 (s, 3H), 2.20 (s, 3H), 1.43 (s, 6H); ^{13}C NMR: δ 192.9, 158.7, 147.0, 129.7, 126.9, 119.3, 118.4, 79.4, 49.3, 27.1, 20.9, 19.2; HRMS (ESI) *m/z* Calcd for $[C_{13}H_{16}O_2 + H]^+$: 205.1229; found: 205.1228.

2,2,6,8-Tetramethyl-4-chromanone (**71j**): Yield: 155 mg (0.76 mmol, 76%) as a white solid, mp 63-65 °C; IR: 1689, 1614 cm^{-1}; ^1H NMR: δ 7.51 (s, 1H), 7.16 (s, 1H), 2.69 (s, 2H), 2.26 (s, 3H), 2.18 (s, 3H), 1.44 (s, 6H); ^{13}C NMR: δ 193.3, 156.3, 138.1, 129.2, 127.3, 123.6, 119.4, 78.6, 49.8, 26.7, 20.3, 15.7; HRMS (ESI) *m/z* Calcd for $[C_{13}H_{16}O_2 + H]^+$: 205.1229; found: 205.1221.

2,2,7,8-Tetramethyl-4-chromanone (**71k**): Yield: 177 mg (0.87 mmol, 87%) as a white solid, mp 52-54 °C; IR: 1688, 1604 cm^{-1}; ^1H NMR: δ 7.62 (d, *J* = 8.0 Hz, 1H), 6.78 (d, *J* = 8.0 Hz, 1H),

2.67 (s, 2H), 2.29 (s, 3H), 2.14 (s, 3H), 1.45 (s, 6H); ^{13}C NMR: δ 193.5, 158.3, 146.0, 125.9, 123.7, 122.7, 118.5, 49.1, 27.3, 21.2, 11.9; HRMS (ESI) *m/z* Calcd for $[C_{13}H_{16}O_2 + H]^+$: 205.1229; found: 205.1233.

3,3-Dimethyl-2,3-dihydro-1*H*-benzo[*f*]chromen-1-one (**71l**): Yield: 174 mg (0.77 mmol, 77%) as a light yellow solid, mp 78-80 °C; IR: 1672, 1618 cm^{-1}; ^{1}H NMR: δ 9.44 (d, *J* = 8.7 Hz, 1H), 7.89 (d, *J* = 9.0 Hz, 1H), 7.72 (d, *J* = 8.0 Hz, 1H), 7.61 (t, *J* = 7.9 Hz, 1H), 7.40 (t, *J* = 7.5 Hz, 1H), 7.05 (d, *J* = 9.0 Hz, 1H), 2.82 (s, 2H), 1.51 (s, 6H); ^{13}C NMR: δ 193.6, 162.0, 137.3, 131.3, 129.5, 128.8, 128.3, 125.5, 124.5, 119.4, 111.4, 79.4, 50.1, 26.3; HRMS (ESI) *m/z* Calcd for $[C_{15}H_{14}O_2 + H]^+$: 227.1072; found: 227.1068.

2,2-Dimethyl-2,3,6,7,8,9-hexahydro-4*H*-benzo[*g*]chromen-4-one (**71m**): Yield: 193 mg (0.84 mmol, 84%) as a white solid, mp 75-76 °C; IR: 1687, 1618 cm^{-1}; ^{1}H NMR: δ 7.56 (s, 1H), 6.63 (s, 1H), 2.76 (m, 4H), 2.67 (s, 2H), 1.77 (m, 4H), 1.43 (s, 6H); ^{13}C NMR: δ 192.6, 157.6, 147.1, 129.9, 126.3, 118.2, 117.7, 78.8, 49.0, 30.7, 28.4, 26.7, 23.2, 22.7; HRMS (ESI) *m/z* Calcd for $[C_{15}H_{18}O_2 + H]^+$: 231.1385; found: 231.1377.

7-Chloro-2,2-dimethyl-4-chromanone (**71n**): Yield: 84 mg (0.40 mmol, 40%; 48% brsm) as a white solid, mp 69-70 °C; IR: 1694, 1599 cm^{-1}; ^{1}H NMR: δ 7.79 (d, *J* = 9.0 Hz, 1H), 6.95 (m, 2H), 2.71 (s, 2H), 1.46 (s, 6H); ^{13}C NMR: δ 191.5, 160.4, 141.9, 127.8, 121.5, 118.7, 118.5, 80.0, 48.7, 26.6; HRMS (ESI) *m/z* Calcd for $[C_{11}H_{11}ClO_2 + H]^+$: 211.0526; found: 211.0529. A faster moving band contained 3-chlorophenyl 3-methyl-2-butenoate [**68n** (X = 3-Cl), 55 mg, 0.26 mmol, 26%; 31% brsm] as a colorless oil. IR: 1742, 1649 cm^{-1}; ^{1}H NMR: δ 7.30 (t, *J* = 8.1 Hz, 1H), 7.20 (dm, *J* = 9.0 Hz, 1H), 7.15 (t, *J* = 2.4 Hz, 1H), 7.01 (dm, *J* = 8.1 Hz, 1H), 5.89 (s, 1H), 2.24 (s, 3H), 2.00 (s, 3H); ^{13}C NMR: δ 164.4, 160.9, 151.2, 134.6, 130.1, 125.8, 122.5, 120.2, 114.8, 27.7, 20.6; HRMS (ESI) *m/z* Calcd for $[C_{11}H_{11}ClO_2 + H]^+$: 211.0526; found: 211.0520.

6-Methoxy-2,2-dimethyl-4-chromanone (**71o**): Yield: 165 mg (0.80 mmol, 80%) as a light yellow solid, mp 69-71 °C; IR: 2834, 1686, 1619 cm^{-1}; ^{1}H NMR: δ 7.29 (s, 1H), 7.08 (d, *J* = 9.0

Hz, 1H), 6.85 (d, *J* = 9.0 Hz, 1H), 3.79 (s, 3H), 2.70 (s, 2H), 1.44 (s, 6H); ^{13}C NMR: δ 193.1, 155.1, 154.0, 125.8, 120.4, 120.1, 107.4, 79.5, 56.2, 49.3, 27.0; HRMS (ESI) *m/z* Calcd for $[C_{12}H_{14}O_3 + H]^+$: 207.1021; found: 207.1015.

(±)-2,6-Dimethyl-4-chromanone (**73b**): Yield: 114 mg (0.65 mmol, 65%) as a yellow oil; IR: 1691, 1618 cm^{-1}; ^{1}H NMR: δ 7.67 (d, *J* = 2.4 Hz, 1H), 7.28 (dd, *J* = 8.4, 2.4 Hz, 1H), 6.87 (d, *J* = 8.4 Hz, 1H), 4.55 (m, 1H), 2.67 (AB pattern, *J* = 16.9 Hz, 1H), 2.65 (s, 1H), 2.30 (s, 3H), 1.51 (d, *J* = 6.3 Hz, 3H); ^{13}C NMR: δ 192.8, 159.8, 137.1, 130.6, 126.5, 120.4, 117.7, 74.2, 44.7, 21.0, 20.4; HRMS (ESI) *m/z* Calcd for $[C_{11}H_{12}O_2 + H]^+$: 177.0916; found: 177.0913.

(±)-2,7-Dimethyl-4-chromanone (**73c**): Yield: 91 mg (0.52 mmol, 52%) as a light yellow oil; IR: 1689, 1615 cm^{-1}; ^{1}H NMR: δ 7.77 (d, *J* = 8.0 Hz, 1H), 6.82 (d, *J* = 8.0 Hz, 1H), 6.77 (s, 1H), 4.56 (m, 1H), 2.66 (AB pattern, *J* = 16.5 Hz, 1H), 2.64 (s, 1H), 2.35 (s, 3H), 1.50 (d, *J* = 6.3 Hz, 3H); ^{13}C NMR: δ 192.3, 161.7, 147.5, 126.8, 122.6, 118.6, 117.9, 74.3, 44.6, 21.9, 21.0; HRMS (ESI) *m/z* Calcd for $[C_{11}H_{12}O_2 + H]^+$: 177.0916; found: 177.0921.

(±)-2,5,7-Trimethyl-4-chromanone (**73d**): Yield: 159 mg (0.84 mmol, 84%) as a white solid, mp 53-54 ^{o}C; IR: 1681, 1613 cm^{-1}; ^{1}H NMR: δ 6.64 (s, 1H), 6.60 (s, 1H), 4.51 (m, 1H), 2.65-2.58 (obscured pattern, 2H), 2.60 (s, 3H), 2.29 (s, 3H), 1.47 (d, *J* = 6.3 Hz, 3H); ^{13}C NMR: δ 193.6, 162.8, 145.8, 141.8, 125.8, 117.1, 115.9, 73.5, 46.1, 22.7, 21.7, 20.9; HRMS (ESI) *m/z* Calcd for $[C_{12}H_{14}O_2 + H]^+$: 191.1072; found: 191.1070.

(±)-2,5-Dimethyl-8-isopropyl-4-chromanone (**73e**): Yield: 72 mg (0.33 mmol, 33%; 40% brsm) as a white solid, mp 64-65 ^{o}C; IR: 1685, 1579 cm^{-1}; ^{1}H NMR: δ 7.24 (d, *J* = 7.8 Hz, 1H), 6.75 (d, *J* = 7.7 Hz, 1H), 4.52 (m 1H), 3.28 (septet, *J* = 6.9 Hz, 1H), 2.68 (AB pattern, *J* = 16.8 Hz, 1H), 2.65 (s, 1H), 2.60 (s, 3H), 1.51 (d, *J* = 6.2 Hz, 3H), 1.21 (d, *J* = 6.9 Hz, 6H); ^{13}C NMR: δ 195.1, 160.5, 139.5, 135.5, 131.7, 124.5, 119.8, 73.8, 46.6, 27.2, 23.2, 23.0, 22.9, 21.4; HRMS (ESI) *m/z* Calcd for $[C_{14}H_{18}O_2 + H]^+$: 219.1385; found: 219.1388. A faster moving band contained 2-isopropyl-5-methylphenyl (*E*)-2-butenoate [**79e** (X = 2-*i*-Pr-5-Me), 72 mg, 0.33

mmol, 33%; 40% brsm] as a light yellow oil; IR: 1739, 1659 cm^{-1}; ^1H NMR: δ 7.24-7.14 (complex, 2H), 7.02 (d, *J* = 7.9 Hz, 1H), 6.83 (s, 1H), 6.07 (dd, *J* = 15.5, 1.5 Hz, 1H), 2.98 (septet, *J* = 6.9 Hz, 1H), 2.32 (s, 3H), 1.97 (dd, *J* = 7.0, 1.8 Hz, 3H), 1.19 (d, *J* = 6.9 Hz, 6H); ^{13}C NMR: δ 165.1, 147.9, 146.7, 137.1, 136.5, 127.0, 126.4, 122.8, 122.1, 27.1, 23.0, 20.8, 18.2; HRMS (ESI) *m/z* Calcd for $[C_{14}H_{18}O_2 + H]^+$: 219.1385; found: 219.1378.

(±)-7-Fluoro-2-methyl-4-chromanone (**73f**): Yield: 128 mg (0.71 mmol, 71%) as a light yellow oil; IR: 1695, 1612 cm^{-1}; ^1H NMR: δ 7.89 (dd, *J* = 8.8, 6.6 Hz, 1H), 6.72 (td, *J* = 8.4, 2.4 Hz, 1H), 6.65 (dd, *J* = 10.1, 2.4 Hz, 1H), 4.61 (m, 1H), 2.68 (s, 1H), 2.66 (AB, *J* = 16.4 Hz, 1H), 1.51 (d, *J* = 6.3 Hz, 3H); ^{13}C NMR: δ 191.1, 167.4 (d, *J* = 256.0 Hz), 163.3 (d, *J* = 13.7 Hz), 129.4 (d, *J* = 11.4 Hz), 117.7 (d, *J* = 2.6 Hz), 109.6 (d, *J* = 22.7 Hz), 104.6 (d, *J* = 24.3 Hz), 74.9, 44.1, 20.8; HRMS (ESI) *m/z* Calcd for $[C_{10}H_9FO_2 + H]^+$: 181.0664; found: 181.0661.

(±)-7-Methoxy-2-methyl-4-chromanone (**73g**): Yield: 105 mg (0.55 mmol, 55%) as a yellow solid, mp 67-69 °C; IR: 2839, 1682, 1607 cm^{-1}; ^1H NMR: δ 7.52 (d, *J* = 8.8 Hz, 1H), 6.57 (dd, *J* = 8.8, 2.4 Hz, 1H), 6.42 (d, *J* = 2.4 Hz, 1H), 4.59 (m, 1H), 3.83 (s, 3H), 2.64 (AB, *J* = 16.8 Hz, 1H), 2.62 (s, 1H), 1.51 (d, *J* = 6.3 Hz, 3H); ^{13}C NMR: δ 191.1, 166.0, 163.6, 128.7, 114.8, 109.8, 100.7, 74.7, 55.6, 44.3, 21.0; HRMS (ESI) *m/z* Calcd for $[C_{11}H_{12}O_3 + H]^+$: 193.0865; found: 193.0859.

(±)-2,5,8-Trimethyl-4-chromanone (**73h**): Yield: 80 mg (0.42 mmol, 42%; 47% brsm) as a light yellow oil; IR: 1685, 1583 cm^{-1}; ^1H NMR: δ 7.17 (d, *J* = 7.5 Hz, 1H), 6.68 (d, *J* = 7.5 Hz, 1H), 4.53 (m, 1H), 2.67 (AB pattern, *J* = 16.6 Hz, 1H), 2.64 (s, 1H), 2.59 (s, 3H), 2.19 (s, 3H), 1.50 (d, *J* = 6.3 Hz, 3H); ^{13}C NMR: □ 194.9, 161.3, 139.6, 135.9, 125.1, 124.0, 118.8, 73.8, 46.5, 23.2, 21.4, 16.3; HRMS (ESI) *m/z* Calcd for $[C_{12}H_{14}O_2 + H]^+$: 191.1072; found: 191.1066. A faster moving band contained 2,5-dimethylphenyl (*E*)-2-butenoate [**79h** (X = 2,5-diMe), 67 mg, 0.35 mmol, 35%; 39% brsm] as a colorless oil; IR: 1739, 1656 cm^{-1}; ^1H NMR: □ 7.16 (dq, *J* = 15.5, 6.9 Hz, 1H), 7.10 (d, *J* = 7.7 Hz, 1H), 6.94 (d, *J* = 7.7 Hz, 1H), 6.84 (s, 1H), 6.07 (dq, *J* =

15.5, 1.7 Hz, 1H), 2.31 (s, 3H), 2.12 (s, 3H), 1.96 (dd, *J* = 6.9, 1.7 Hz, 3H); ^{13}C NMR: δ 164.7, 149.2, 146.7, 136.8, 130.8, 127.0, 126.7, 122.5, 122.0, 20.9, 18.2, 15.8; HRMS (ESI) *m/z* Calcd for $[C_{12}H_{14}O_2 + H]^+$: 191.1072; found: 191.1062.

(±)-2,6,7-Trimethyl-4-chromanone (**73i**): Yield: 136 mg (0.72 mmol, 72%) as a tan solid, mp 73-75 °C; IR: 1681, 1621 cm^{-1}; ^{1}H NMR: δ 7.61 (s, 1H), 6.76 (s, 1H), 4.55 (m, 1H), 2.64 (AB pattern, *J* = 16.9 Hz, 1H), 2.62 (s, 1H), 2.26 (s, 3H), 2.21 (s, 3H), 1.49 (d, *J* = 6.3 Hz, 3H); ^{13}C NMR: δ 192.5, 160.0 146.5, 129.8, 126.9, 118.6, 118.3, 74.2, 44.6, 21.0, 20.5, 18.8; HRMS (ESI) *m/z* Calcd for $[C_{12}H_{14}O_2 + H]^+$: 191.1072; found: 191.1075.

(±)-2,6,8-Trimethyl-4-chromanone (**73j**): Yield: 68 mg (0.36 mmol, 36%; 44% brsm) as a light yellow solid, mp 48-51 °C; IR: 1692,1616 cm^{-1}; ^{1}H NMR: δ 7.53 (s, 1H), 7.16 (s, 1H), 4.54 (m, 1H), 2.65 (apparent s, 1H), 2.63 (s, 1H), 2.26 (s, 3H), 2.21 (s, 3H), 1.52 (d, *J* = 6.3 Hz, 3H); ^{13}C NMR: δ 193.2, 158.1, 138.0, 129.8, 126.8, 124.0, 120.1, 74.0, 44.6, 21.0, 20.4, 15.6; HRMS (ESI) *m/z* Calcd for $[C_{12}H_{14}O_2 + H]^+$: 191.1072; found: 191.1064. A faster moving band contained 2,4-dimethylphenyl (*E*)-2-butenoate [**79j** (X = 2,4-diMe), 57 mg, 0.30 mmol, 30%; 37% brsm] as a light yellow oil; IR: 1740, 1657 cm^{-1}; ^{1}H NMR: δ 7.19 (dq, *J* = 16.9, 6.9 Hz, 1H), 7.03 (s, 1H), 7.00 (d, *J* = 8.1 Hz, 1H), 6.90 (d, *J* = 8.1 Hz, 1H), 6.07 (dd, *J* = 16.9, 1.8 Hz, 1H), 2.30 (s, 3H), 2.13 (s, 3H), 1.96 (dd, *J* = 6.9, 1.8 Hz, 3H); ^{13}C NMR: δ 164.8, 147.1, 146.6, 135.4, 131.7, 129.8, 127.4, 122.0, 121.6, 20.8, 18.2, 16.1; HRMS (ESI) *m/z* Calcd for $[C_{12}H_{14}O_2 + H]^+$: 191.1072; found: 191.1066.

(±)-2,7,8-Trimethyl-4-chromanone (**73k**): Yield: 152 mg (0.80 mmol, 80%) as a yellow oil; IR: 1688, 1604 cm^{-1}; ^{1}H NMR: δ 7.66 (d, *J* = 8.0 Hz, 1H), 6.82 (d, *J* = 8.0 Hz, 1H), 4.55 (m, 1H), 2.65 (s, 1H), 2.63 (AB, *J* = 16.5 Hz, 1H), 2.30 (s, 3H), 2.16 (s, 3H), 1.53 (d, *J* = 6.3 Hz, 3H); ^{13}C NMR: δ 192.8, 159.5, 145.3, 124.9, 123.5, 122.6, 118.5, 73.9, 44.2, 20.9, 20.5, 11.2; HRMS (ESI) *m/z* Calcd for $[C_{12}H_{14}O_2 + H]^+$: 191.1072; found: 191.1067.

(±)-3-Methyl-2,3-dihydro-1*H*-benzo[*f*]chromen-1-one (**73l**): Yield: 159 mg (0.75 mmol, 75%) as a white solid, mp 66-68 °C; IR: 1667, 1618 cm^{-1}; ^1H NMR: δ 9.45 (d, *J* = 8.1 Hz, 1H), 7.91 (d, *J* = 9.0 Hz, 1H), 7.74 (d, *J* = 8.1 Hz, 1H), 7.63 (d, *J* = 7.8 Hz, 1H), 7.42 (t, *J* = 7.5 Hz, 1H), 7.10 (d, *J* = 9.0 Hz, 1H), 4.71 (m, 1H), 2.87-2.69 (complex, 2H), 1.57 (d, *J* = 6.0 Hz, 3H); ^{13}C NMR: δ 193.4, 163.6, 137.2, 131.1, 129.4, 128.9, 128.1, 125.6, 124.6, 118.7, 112.2, 74.2, 45.6, 20.5; HRMS (ESI) *m/z* Calcd for $[C_{14}H_{12}O_2 + H]^+$: 213.0916; found: 213.0909.

(±)-2-Methyl-2,3,6,7,8,9-hexahydro-4*H*-benzo[*g*]chromen-4-one (**73m**): Yield: 112 mg (0.52 mmol, 52%) as a light yellow solid, mp 60-61 °C; IR: 1686, 1618 cm^{-1}; ^1H NMR: δ 7.58 (s, 1H), 6.67 (s, 1H), 4.51 (m, 1H), 2.72 (dm, *J* = 15.8 Hz, 4H), 2.64 (AB, *J* = 15.8 Hz, 1H), 2.62 (s, 1H), 1.77 (m, 4H), 1.48 (d, *J* = 6.3 Hz, 3H); ^{13}C NMR: δ 192.6, 159.3, 146.9, 130.5, 126.7, 118.8, 117.2, 74.1, 44.7, 30.1, 28.5, 23.1, 22.7, 21.0; HRMS (ESI) *m/z* Calcd for $[C_{14}H_{16}O_2 + H]^+$: 217.1229; found: 217.1232.

(±)-7-Chloro-2-methyl-4-chromanone (**73n**): Yield: 52 mg (0.26 mmol, 36%; 46% brsm) as a white solid, mp 53-55 °C; IR: 1690, 1598 cm^{-1}; ^1H NMR: δ 7.81 (d, *J* = 8.2 Hz, 1H), 7.00 (s, 1 H), 6.99 (dd, *J* = 8.2, 2.0 Hz, 1H), 4.61 (m, 1H), 2.69 (s, 1H), 2.67 (AB pattern, *J* = 16.8 Hz, 1H), 1.52 (d, *J* = 6.3 Hz, 3H),; ^{13}C NMR: δ 191.2, 161.8, 141.6, 128.0, 121.9, 119.2, 117.9, 74.7, 44.2, 20.7; HRMS (ESI) *m/z* Calcd for $[C_{10}H_9ClO_2 + H]^+$: 197.0369; found: 197.0376. A faster moving band contained 3-chlorophenyl (*E*)-2-butenoate [**79n** (X = 3-Cl), 43 mg, 0.22 mmol, 22%; 28% brsm] as a light yellow oil; IR: 1736, 1655 cm^{-1}; ^1H NMR: δ 7.30 (t, *J* = 8.1 Hz, 1H), 7.24-7.14 (complex, 3H), 7.03 (d, *J* = 8.2 Hz, 1H), 6.03 (d, *J* = 15.5 Hz, 1H), 1.98 (dd, *J* = 6.9, 1.7 Hz, 3H); ^{13}C NMR: δ 164.2, 151.1, 147.4, 134.4, 129.9, 125.8, 122.2, 121.5, 119.9, 18.1; HRMS (ESI) *m/z* Calcd for $[C_{10}H_9ClO_2 + H]^+$: 197.0369; found: 197.0362.

(±)-6-Methoxy-2-methyl-4-chromanone (**73o**): Yield: 99 mg (0.52 mmol, 52%) as an orange solid, mp 58-61 °C; IR: 2834, 1689, 1621 cm^{-1}; ^1H NMR: δ 7.31 (d, *J* = 3.2 Hz, 1H), 7.09 (dd, *J* = 9.0, 3.2 Hz, 1H), 6.91 (d, *J* = 9.0 Hz, 1H), 4.55 (m, 1H), 3.80 (s, 3H), 2.67 (apparent br s, 1H),

2.65 (s, 1H), 1.51 (d, J = 6.3 Hz, 3H); ^{13}C NMR: δ 193.1, 156.9, 154.4, 125.7, 121.7, 119.6, 107.7, 74.8, 56.3, 45.0, 21.4; HRMS (ESI) *m/z* Calcd for $[C_{11}H_{12}O_3 + H]^+$: 193.0865; found: 193.0866.

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APPENDICES

Appendix A: X-ray data for ethyl (*E*)-4-{3-oxo-3-[(2,2,4,4-tetramethylthiochroman-6-yl)amino]prop-1-en-1-yl}benzoate (31a)

Table 1. Crystal data and structure refinement for 14078.

Empirical formula	$C_{25}\ H_{29}\ N\ O_3\ S$	
Formula weight	423.55	
Crystal system	triclinic	
Space group	$P\bar{1}$	
Unit cell dimensions	a = 7.4097(15) Å	α= 98.377(3)°
	b = 7.8663(16) Å	β= 92.751(4)°
	c = 19.553(3) Å	γ= 104.530(3)°
Volume	1087.2(4) $Å^3$	
Z, Z'	2, 1	
Density (calculated)	1.294 Mg/m^3	
Wavelength	0.71073 Å	
Temperature	100(2) K	
F(000)	452	
Absorption coefficient	0.176 mm^{-1}	
Absorption correction	semi-empirical from equivalents	
Max. and min. transmission	0.996 and 0.954	
Theta range for data collection	2.114 to 30.721°	
Reflections collected	12709	
Independent reflections	6264 [R(int) = 0.0283]	
Data / restraints / parameters	6264 / 0 / 274	
$wR(F^2$ all data)	$wR2$ = 0.1222	
$R(F$ obsd data)	$R1$ = 0.0466	
Goodness-of-fit on F^2	1.000	
Observed data [I > 2σ(I)]	4573	
Largest and mean shift / s.u.	0.001and 0.000	
Largest diff. peak and hole	0.452 and -0.286 $e/Å^3$	

$wR2 = \{ \Sigma [w(F_o^2 - F_c^2)^2] / \Sigma [w(F_o^2)^2] \}^{1/2}$

$R1 = \Sigma ||F_o| - |F_c|| / \Sigma |F_o|$

Table 2. Atomic coordinates and equivalent isotropic displacement parameters for 14078. U(eq) is defined as one third of the trace of the orthogonalized U_{ij} tensor.

	x	y	z	U(eq)
S(1)	0.62988(6)	1.35467(5)	0.83063(2)	0.01910(11)
O(1)	0.21259(16)	0.64505(15)	0.58480(6)	0.0218(3)
O(2)	0.20448(16)	-0.47092(14)	0.34807(6)	0.0208(3)
O(3)	-0.04019(15)	-0.41335(13)	0.29190(6)	0.0173(2)
N(1)	0.49077(19)	0.65542(16)	0.64317(7)	0.0149(3)
C(1)	0.6934(2)	1.29791(19)	0.91405(8)	0.0161(3)
C(2)	0.8612(2)	1.21863(19)	0.90506(8)	0.0164(3)
C(3)	0.8364(2)	1.04283(19)	0.85347(8)	0.0153(3)
C(4)	0.6927(2)	1.01828(18)	0.79122(8)	0.0131(3)
C(5)	0.5984(2)	1.14553(18)	0.77755(8)	0.0142(3)
C(6)	0.4703(2)	1.11091(19)	0.71923(8)	0.0163(3)
C(7)	0.4317(2)	0.95173(19)	0.67340(8)	0.0149(3)
C(8)	0.5228(2)	0.82258(18)	0.68625(8)	0.0134(3)
C(9)	0.6514(2)	0.85829(19)	0.74426(8)	0.0142(3)
C(10)	0.3402(2)	0.57610(19)	0.59567(8)	0.0146(3)
C(11)	0.3423(2)	0.39825(19)	0.55859(8)	0.0154(3)
C(12)	0.2137(2)	0.31937(19)	0.50573(8)	0.0147(3)
C(13)	0.1889(2)	0.14210(19)	0.46446(8)	0.0134(3)
C(14)	0.2724(2)	0.01513(19)	0.48550(8)	0.0154(3)
C(15)	0.2436(2)	-0.15158(19)	0.44524(8)	0.0159(3)
C(16)	0.1292(2)	-0.19464(18)	0.38334(8)	0.0137(3)
C(17)	0.0411(2)	-0.07079(19)	0.36262(8)	0.0149(3)
C(18)	0.0712(2)	0.09640(19)	0.40287(8)	0.0143(3)
C(19)	0.1045(2)	-0.37270(19)	0.34073(8)	0.0148(3)
C(20)	0.7526(3)	1.4745(2)	0.96421(9)	0.0217(4)
C(21)	0.5256(3)	1.1746(2)	0.93918(9)	0.0237(4)
C(22)	1.0295(2)	1.0480(2)	0.82694(9)	0.0223(4)
C(23)	0.7817(3)	0.8832(2)	0.89272(9)	0.0227(4)
C(24)	-0.0757(2)	-0.58813(19)	0.24943(9)	0.0193(3)
C(25)	-0.2311(2)	-0.6024(2)	0.19472(9)	0.0230(4)

Table 3. Bond lengths [Å] and angles [°] for 14078.

S(1)-C(5)	1.7678(15)	C(12)-H(12)	0.9500
S(1)-C(1)	1.8236(16)	C(13)-C(14)	1.398(2)
O(1)-C(10)	1.2265(18)	C(13)-C(18)	1.398(2)
O(2)-C(19)	1.2148(18)	C(14)-C(15)	1.388(2)
O(3)-C(19)	1.3431(18)	C(14)-H(14)	0.9500
O(3)-C(24)	1.4540(17)	C(15)-C(16)	1.391(2)
N(1)-C(10)	1.3710(19)	C(15)-H(15)	0.9500
N(1)-C(8)	1.4131(18)	C(16)-C(17)	1.396(2)
N(1)-H(1)	0.866(19)	C(16)-C(19)	1.485(2)
C(1)-C(21)	1.524(2)	C(17)-C(18)	1.390(2)
C(1)-C(20)	1.530(2)	C(17)-H(17)	0.9500
C(1)-C(2)	1.531(2)	C(18)-H(18)	0.9500
C(2)-C(3)	1.553(2)	C(20)-H(20A)	0.9800
C(2)-H(2A)	0.9900	C(20)-H(20B)	0.9800
C(2)-H(2B)	0.9900	C(20)-H(20C)	0.9800
C(3)-C(4)	1.535(2)	C(21)-H(21A)	0.9800
C(3)-C(22)	1.538(2)	C(21)-H(21B)	0.9800
C(3)-C(23)	1.545(2)	C(21)-H(21C)	0.9800
C(4)-C(9)	1.4012(19)	C(22)-H(22A)	0.9800
C(4)-C(5)	1.405(2)	C(22)-H(22B)	0.9800
C(5)-C(6)	1.397(2)	C(22)-H(22C)	0.9800
C(6)-C(7)	1.386(2)	C(23)-H(23A)	0.9800
C(6)-H(6)	0.9500	C(23)-H(23B)	0.9800
C(7)-C(8)	1.397(2)	C(23)-H(23C)	0.9800
C(7)-H(7)	0.9500	C(24)-C(25)	1.505(2)
C(8)-C(9)	1.394(2)	C(24)-H(24A)	0.9900
C(9)-H(9)	0.9500	C(24)-H(24B)	0.9900
C(10)-C(11)	1.483(2)	C(25)-H(25A)	0.9800
C(11)-C(12)	1.335(2)	C(25)-H(25B)	0.9800
C(11)-H(11)	0.9500	C(25)-H(25C)	0.9800
C(12)-C(13)	1.469(2)		

C(5)-S(1)-C(1)	99.55(7)	C(2)-C(1)-S(1)	107.38(11)
C(19)-O(3)-C(24)	115.44(12)	C(1)-C(2)-C(3)	118.80(13)
C(10)-N(1)-C(8)	126.48(13)	C(1)-C(2)-H(2A)	107.6
C(10)-N(1)-H(1)	117.6(12)	C(3)-C(2)-H(2A)	107.6
C(8)-N(1)-H(1)	115.9(12)	C(1)-C(2)-H(2B)	107.6
C(21)-C(1)-C(20)	109.62(13)	C(3)-C(2)-H(2B)	107.6
C(21)-C(1)-C(2)	113.77(13)	H(2A)-C(2)-H(2B)	107.0
C(20)-C(1)-C(2)	109.67(13)	C(4)-C(3)-C(22)	109.03(13)
C(21)-C(1)-S(1)	110.49(12)	C(4)-C(3)-C(23)	109.74(12)
C(20)-C(1)-S(1)	105.57(10)	C(22)-C(3)-C(23)	108.03(13)

C(4)-C(3)-C(2)	114.18(12)	C(16)-C(17)-H(17)	120.0
C(22)-C(3)-C(2)	106.26(12)	C(17)-C(18)-C(13)	120.60(14)
C(23)-C(3)-C(2)	109.38(13)	C(17)-C(18)-H(18)	119.7
C(9)-C(4)-C(5)	117.01(14)	C(13)-C(18)-H(18)	119.7
C(9)-C(4)-C(3)	118.36(13)	O(2)-C(19)-O(3)	123.14(13)
C(5)-C(4)-C(3)	124.62(13)	O(2)-C(19)-C(16)	124.36(14)
C(6)-C(5)-C(4)	120.36(13)	O(3)-C(19)-C(16)	112.49(13)
C(6)-C(5)-S(1)	115.70(11)	C(1)-C(20)-H(20A)	109.5
C(4)-C(5)-S(1)	123.95(12)	C(1)-C(20)-H(20B)	109.5
C(7)-C(6)-C(5)	121.66(14)	H(20A)-C(20)-H(20B)	109.5
C(7)-C(6)-H(6)	119.2	C(1)-C(20)-H(20C)	109.5
C(5)-C(6)-H(6)	119.2	H(20A)-C(20)-H(20C)	109.5
C(6)-C(7)-C(8)	118.99(14)	H(20B)-C(20)-H(20C)	109.5
C(6)-C(7)-H(7)	120.5	C(1)-C(21)-H(21A)	109.5
C(8)-C(7)-H(7)	120.5	C(1)-C(21)-H(21B)	109.5
C(9)-C(8)-C(7)	119.11(13)	H(21A)-C(21)-H(21B)	109.5
C(9)-C(8)-N(1)	117.73(13)	C(1)-C(21)-H(21C)	109.5
C(7)-C(8)-N(1)	123.16(14)	H(21A)-C(21)-H(21C)	109.5
C(8)-C(9)-C(4)	122.87(14)	H(21B)-C(21)-H(21C)	109.5
C(8)-C(9)-H(9)	118.6	C(3)-C(22)-H(22A)	109.5
C(4)-C(9)-H(9)	118.6	C(3)-C(22)-H(22B)	109.5
O(1)-C(10)-N(1)	123.10(13)	H(22A)-C(22)-H(22B)	109.5
O(1)-C(10)-C(11)	122.31(14)	C(3)-C(22)-H(22C)	109.5
N(1)-C(10)-C(11)	114.59(13)	H(22A)-C(22)-H(22C)	109.5
C(12)-C(11)-C(10)	119.05(14)	H(22B)-C(22)-H(22C)	109.5
C(12)-C(11)-H(11)	120.5	C(3)-C(23)-H(23A)	109.5
C(10)-C(11)-H(11)	120.5	C(3)-C(23)-H(23B)	109.5
C(11)-C(12)-C(13)	127.09(14)	H(23A)-C(23)-H(23B)	109.5
C(11)-C(12)-H(12)	116.5	C(3)-C(23)-H(23C)	109.5
C(13)-C(12)-H(12)	116.5	H(23A)-C(23)-H(23C)	109.5
C(14)-C(13)-C(18)	118.70(13)	H(23B)-C(23)-H(23C)	109.5
C(14)-C(13)-C(12)	122.75(14)	O(3)-C(24)-C(25)	107.39(13)
C(18)-C(13)-C(12)	118.51(13)	O(3)-C(24)-H(24A)	110.2
C(15)-C(14)-C(13)	120.87(14)	C(25)-C(24)-H(24A)	110.2
C(15)-C(14)-H(14)	119.6	O(3)-C(24)-H(24B)	110.2
C(13)-C(14)-H(14)	119.6	C(25)-C(24)-H(24B)	110.2
C(14)-C(15)-C(16)	120.00(14)	H(24A)-C(24)-H(24B)	108.5
C(14)-C(15)-H(15)	120.0	C(24)-C(25)-H(25A)	109.5
C(16)-C(15)-H(15)	120.0	C(24)-C(25)-H(25B)	109.5
C(15)-C(16)-C(17)	119.72(13)	H(25A)-C(25)-H(25B)	109.5
C(15)-C(16)-C(19)	118.68(13)	C(24)-C(25)-H(25C)	109.5
C(17)-C(16)-C(19)	121.60(14)	H(25A)-C(25)-H(25C)	109.5
C(18)-C(17)-C(16)	120.07(14)	H(25B)-C(25)-H(25C)	109.5
C(18)-C(17)-H(17)	120.0		

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for 14078. The anisotropic displacement factor exponent takes the form:
$-2\pi^2[\ h^2 a^{*2} U_{11} + ... + 2\ h\ k\ a^*\ b^*\ U_{12}\ ]$

	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
S(1)	26(1)	11(1)	20(1)	-1(1)	-3(1)	7(1)
O(1)	18(1)	20(1)	27(1)	-6(1)	-7(1)	10(1)
O(2)	17(1)	16(1)	30(1)	0(1)	0(1)	8(1)
O(3)	15(1)	13(1)	22(1)	-3(1)	-3(1)	4(1)
N(1)	12(1)	14(1)	18(1)	-2(1)	-1(1)	4(1)
C(1)	17(1)	12(1)	18(1)	0(1)	1(1)	3(1)
C(2)	16(1)	13(1)	17(1)	-1(1)	-3(1)	2(1)
C(3)	16(1)	12(1)	18(1)	0(1)	-1(1)	4(1)
C(4)	11(1)	13(1)	14(1)	1(1)	2(1)	2(1)
C(5)	15(1)	11(1)	16(1)	1(1)	2(1)	2(1)
C(6)	17(1)	14(1)	20(1)	3(1)	0(1)	6(1)
C(7)	15(1)	13(1)	16(1)	1(1)	-1(1)	3(1)
C(8)	11(1)	12(1)	17(1)	1(1)	2(1)	2(1)
C(9)	12(1)	12(1)	19(1)	0(1)	1(1)	5(1)
C(10)	12(1)	15(1)	16(1)	-1(1)	1(1)	3(1)
C(11)	14(1)	14(1)	18(1)	-1(1)	1(1)	5(1)
C(12)	14(1)	14(1)	16(1)	1(1)	2(1)	3(1)
C(13)	9(1)	14(1)	16(1)	0(1)	2(1)	3(1)
C(14)	14(1)	16(1)	15(1)	1(1)	-1(1)	3(1)
C(15)	13(1)	15(1)	20(1)	3(1)	0(1)	5(1)
C(16)	11(1)	12(1)	18(1)	1(1)	3(1)	3(1)
C(17)	13(1)	15(1)	16(1)	0(1)	0(1)	4(1)
C(18)	13(1)	14(1)	16(1)	2(1)	1(1)	5(1)
C(19)	11(1)	13(1)	20(1)	2(1)	2(1)	2(1)
C(20)	26(1)	16(1)	21(1)	-4(1)	1(1)	6(1)
C(21)	23(1)	18(1)	27(1)	0(1)	8(1)	2(1)
C(22)	17(1)	21(1)	27(1)	-5(1)	-4(1)	8(1)
C(23)	33(1)	15(1)	19(1)	2(1)	-4(1)	7(1)
C(24)	19(1)	12(1)	24(1)	-3(1)	0(1)	3(1)
C(25)	23(1)	18(1)	23(1)	0(1)	-2(1)	0(1)

Table 5. Hydrogen coordinates and isotropic displacement parameters for 14078.

	x	y	z	U(eq)
H(1)	0.577(3)	0.600(2)	0.6467(9)	0.018
H(2A)	0.9038	1.1984	0.9512	0.020
H(2B)	0.9638	1.3098	0.8905	0.020
H(6)	0.4080	1.1987	0.7108	0.020
H(7)	0.3447	0.9308	0.6338	0.018
H(9)	0.7138	0.7703	0.7523	0.017
H(11)	0.4339	0.3413	0.5722	0.018
H(12)	0.1289	0.3850	0.4935	0.018
H(14)	0.3498	0.0433	0.5279	0.018
H(15)	0.3021	-0.2362	0.4599	0.019
H(17)	-0.0396	-0.1008	0.3210	0.018
H(18)	0.0114	0.1804	0.3884	0.017
H(20A)	0.7813	1.4519	1.0110	0.033
H(20B)	0.6505	1.5332	0.9647	0.033
H(20C)	0.8640	1.5515	0.9491	0.033
H(21A)	0.4807	1.0661	0.9048	0.036
H(21B)	0.4254	1.2350	0.9454	0.036
H(21C)	0.5627	1.1435	0.9835	0.036
H(22A)	1.0222	0.9376	0.7950	0.033
H(22B)	1.1212	1.0597	0.8663	0.033
H(22C)	1.0682	1.1498	0.8026	0.033
H(23A)	0.7818	0.7735	0.8617	0.034
H(23B)	0.6564	0.8741	0.9083	0.034
H(23C)	0.8722	0.9007	0.9330	0.034
H(24A)	-0.1129	-0.6824	0.2784	0.023
H(24B)	0.0385	-0.6020	0.2275	0.023
H(25A)	-0.3411	-0.5821	0.2170	0.035
H(25B)	-0.2633	-0.7215	0.1667	0.035
H(25C)	-0.1899	-0.5129	0.1648	0.035

Table 6. Torsion angles [°] for 14078.

C(5)-S(1)-C(1)-C(21)	-69.37(12)	C(7)-C(8)-C(9)-C(4)	0.7(2)
C(5)-S(1)-C(1)-C(20)	172.18(11)	N(1)-C(8)-C(9)-C(4)	-179.12(14)
C(5)-S(1)-C(1)-C(2)	55.22(11)	C(5)-C(4)-C(9)-C(8)	-0.2(2)
C(21)-C(1)-C(2)-C(3)	59.69(19)	C(3)-C(4)-C(9)-C(8)	179.79(14)
C(20)-C(1)-C(2)-C(3)	-177.14(14)	C(8)-N(1)-C(10)-O(1)	0.5(3)
S(1)-C(1)-C(2)-C(3)	-62.90(15)	C(8)-N(1)-C(10)-C(11)	-178.97(14)
C(1)-C(2)-C(3)-C(4)	30.95(19)	O(1)-C(10)-C(11)-C(12)	8.3(2)
C(1)-C(2)-C(3)-C(22)	151.16(14)	N(1)-C(10)-C(11)-C(12)	-172.25(14)
C(1)-C(2)-C(3)-C(23)	-92.45(16)	C(10)-C(11)-C(12)-C(13)	-177.69(14)
C(22)-C(3)-C(4)-C(9)	65.56(17)	C(11)-C(12)-C(13)-C(14)	14.9(3)
C(23)-C(3)-C(4)-C(9)	-52.58(18)	C(11)-C(12)-C(13)-C(18)	-167.52(15)
C(2)-C(3)-C(4)-C(9)	-175.78(14)	C(18)-C(13)-C(14)-C(15)	1.8(2)
C(22)-C(3)-C(4)-C(5)	-114.42(16)	C(12)-C(13)-C(14)-C(15)	179.32(14)
C(23)-C(3)-C(4)-C(5)	127.43(16)	C(13)-C(14)-C(15)-C(16)	-0.5(2)
C(2)-C(3)-C(4)-C(5)	4.2(2)	C(14)-C(15)-C(16)-C(17)	-1.1(2)
C(9)-C(4)-C(5)-C(6)	-0.2(2)	C(14)-C(15)-C(16)-C(19)	178.74(14)
C(3)-C(4)-C(5)-C(6)	179.77(14)	C(15)-C(16)-C(17)-C(18)	1.5(2)
C(9)-C(4)-C(5)-S(1)	179.63(11)	C(19)-C(16)-C(17)-C(18)	-178.30(14)
C(3)-C(4)-C(5)-S(1)	-0.4(2)	C(16)-C(17)-C(18)-C(13)	-0.3(2)
C(1)-S(1)-C(5)-C(6)	151.30(12)	C(14)-C(13)-C(18)-C(17)	-1.3(2)
C(1)-S(1)-C(5)-C(4)	-28.56(15)	C(12)-C(13)-C(18)-C(17)	-178.99(14)
C(4)-C(5)-C(6)-C(7)	0.1(2)	C(24)-O(3)-C(19)-O(2)	2.5(2)
S(1)-C(5)-C(6)-C(7)	-179.72(13)	C(24)-O(3)-C(19)-C(16)	-178.39(13)
C(5)-C(6)-C(7)-C(8)	0.4(2)	C(15)-C(16)-C(19)-O(2)	-15.5(2)
C(6)-C(7)-C(8)-C(9)	-0.8(2)	C(17)-C(16)-C(19)-O(2)	164.31(16)
C(6)-C(7)-C(8)-N(1)	179.06(14)	C(15)-C(16)-C(19)-O(3)	165.39(13)
C(10)-N(1)-C(8)-C(9)	161.73(15)	C(17)-C(16)-C(19)-O(3)	-14.8(2)
C(10)-N(1)-C(8)-C(7)	-18.1(2)	C(19)-O(3)-C(24)-C(25)	-175.47(13)

Table 7. Hydrogen bonds for 14078[Å and °].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
N(1)-H(1)...O(2)#1	0.866(19)	2.120(19)	2.9857(18)	177.5(18)
C(7)-H(7)...O(1)	0.95	2.26	2.8291(19)	117.7

Symmetry transformations used to generate equivalent atoms:

#1 -x+1, -y, -z+1

Appendices B: X-ray data for 6-acetyl-2-nitrobenzo[4,5]imidazo[2,1-*b*]quinazolin-12(6*H*)-one (26a)

Table 1. Crystal data and structure refinement for GKK/006/070.

Empirical formula	$C_{16}H_{10}N_4O_4$	
Formula weight	322.28	
Crystal system	monoclinic	
Space group	$P2_1$	
Unit cell dimensions	a = 4.940(6) Å	α= 90°
	b = 15.552(18) Å	β= 92.092(16)°
	c = 8.944(10) Å	γ= 90°
Volume	686.7(14) Å^3	
Z, Z'	2, 1	
Density (calculated)	1.559 Mg/m^3	
Wavelength	0.71073 Å	
Temperature	100(2) K	
F(000)	332	
Absorption coefficient	0.116 mm^{-1}	
Absorption correction	semi-empirical from equivalents	
Max. and min. transmission	0.993 and 0.986	
Theta range for data collection	2.279 to 25.973°	
Reflections collected	5819	
Independent reflections	2294 [R(int) = 0.0889]	
Data / restraints / parameters	2294 / 1 / 217	
wR(F^2 all data)	$wR2$ = 0.1906	
R(F obsd data)	$R1$ = 0.0743	
Goodness-of-fit on F^2	0.975	
Observed data [I > 2$^{\cdots\cdot}$(I)]	1436	
Absolute structure parameter	-2.3(10)	
Largest and mean shift / s.u.	0.005 and 0.001	
Largest diff. peak and hole	0.422 and -0.336 e/Å^3	

$wR2 = \{\Sigma[w(F_o^2-F_c^2)^2] / \Sigma [w(F_o^2)^2]\}^{1/2}$

$R1 = \Sigma|| F_o|-|F_c|| / \Sigma |F_o|$

Table 2. Atomic coordinates and equivalent isotropic displacement parameters for GKK/006/070. U(eq) is defined as one third of the trace of the orthogonalized

U_{ij} tensor.

	x	y	z	U(eq)
O(1)	0.2740(10)	0.3343(3)	0.5038(6)	0.0324(14)
O(2)	1.0394(11)	0.4114(3)	0.1677(6)	0.0369(15)
O(3)	1.1275(12)	0.5467(4)	0.1232(6)	0.0380(15)
O(4)	-0.3607(11)	0.6269(4)	0.9290(7)	0.0416(16)
N(1)	0.2381(12)	0.5949(4)	0.6031(8)	0.0267(15)
N(2)	-0.0998(12)	0.5478(4)	0.7748(7)	0.0267(15)
N(3)	0.0994(12)	0.4478(4)	0.6360(7)	0.0237(16)
N(4)	0.9969(13)	0.4895(4)	0.1858(7)	0.0298(17)
C(1)	-0.4138(15)	0.4440(5)	0.9094(9)	0.0294(19)
C(2)	-0.4745(16)	0.3553(5)	0.9197(9)	0.035(2)
C(3)	-0.3455(17)	0.2938(5)	0.8368(10)	0.033(2)
C(4)	-0.1525(16)	0.3173(5)	0.7332(10)	0.0301(19)
C(5)	0.2759(15)	0.4125(5)	0.5301(9)	0.0258(18)
C(6)	0.6347(14)	0.4520(5)	0.3558(8)	0.0229(17)
C(7)	0.7875(15)	0.5145(5)	0.2907(9)	0.0255(19)
C(8)	0.7563(16)	0.6030(5)	0.3231(9)	0.0271(19)
C(9)	0.5742(16)	0.6266(5)	0.4258(8)	0.0283(19)
C(10)	-0.2183(14)	0.4667(5)	0.8101(9)	0.0264(19)
C(11)	-0.0869(15)	0.4044(5)	0.7257(9)	0.029(2)
C(12)	0.0931(14)	0.5355(5)	0.6660(9)	0.0256(18)
C(13)	0.4444(15)	0.4773(4)	0.4609(9)	0.0230(18)
C(14)	0.4139(15)	0.5658(5)	0.4990(9)	0.0229(18)
C(15)	-0.1733(16)	0.6276(5)	0.8456(9)	0.032(2)
C(16)	-0.0100(18)	0.7062(5)	0.8116(11)	0.040(2)

Table 3. Bond lengths [Å] and angles [°] for GKK/006/070.

O(1)-C(5)	1.239(9)	C(3)-H(3)	0.9500
O(2)-N(4)	1.243(8)	C(4)-C(11)	1.395(11)
O(3)-N(4)	1.244(8)	C(4)-H(4)	0.9500
O(4)-C(15)	1.210(10)	C(5)-C(13)	1.459(10)
N(1)-C(12)	1.309(10)	C(6)-C(7)	1.373(10)
N(1)-C(14)	1.373(9)	C(6)-C(13)	1.410(10)
N(2)-C(12)	1.400(9)	C(6)-H(6)	0.9500
N(2)-C(10)	1.431(10)	C(7)-C(8)	1.416(11)
N(2)-C(15)	1.446(10)	C(8)-C(9)	1.359(11)
N(3)-C(12)	1.391(10)	C(8)-H(8)	0.9500
N(3)-C(11)	1.414(10)	C(9)-C(14)	1.410(11)
N(3)-C(5)	1.421(9)	C(9)-H(9)	0.9500
N(4)-C(7)	1.474(10)	C(10)-C(11)	1.403(11)
C(1)-C(10)	1.382(11)	C(13)-C(14)	1.428(10)
C(1)-C(2)	1.416(12)	C(15)-C(16)	1.501(12)
C(1)-H(1)	0.9500	C(16)-H(16A)	0.9799
C(2)-C(3)	1.380(12)	C(16)-H(16B)	0.9800
C(2)-H(2)	0.9500	C(16)-H(16C)	0.9800
C(3)-C(4)	1.402(11)		

C(12)-N(1)-C(14)	115.3(6)	O(1)-C(5)-N(3)	120.3(6)
C(12)-N(2)-C(10)	109.1(6)	O(1)-C(5)-C(13)	126.8(7)
C(12)-N(2)-C(15)	127.6(6)	N(3)-C(5)-C(13)	112.9(7)
C(10)-N(2)-C(15)	123.3(6)	C(7)-C(6)-C(13)	118.4(7)
C(12)-N(3)-C(11)	109.8(6)	C(7)-C(6)-H(6)	120.8
C(12)-N(3)-C(5)	121.7(6)	C(13)-C(6)-H(6)	120.8
C(11)-N(3)-C(5)	128.4(6)	C(6)-C(7)-C(8)	122.4(7)
O(3)-N(4)-O(2)	123.2(7)	C(6)-C(7)-N(4)	119.5(6)
O(3)-N(4)-C(7)	119.0(6)	C(8)-C(7)-N(4)	118.1(7)
O(2)-N(4)-C(7)	117.8(6)	C(9)-C(8)-C(7)	118.7(7)
C(10)-C(1)-C(2)	116.5(7)	C(9)-C(8)-H(8)	120.6
C(10)-C(1)-H(1)	121.8	C(7)-C(8)-H(8)	120.6
C(2)-C(1)-H(1)	121.8	C(8)-C(9)-C(14)	122.0(7)
C(3)-C(2)-C(1)	122.5(7)	C(8)-C(9)-H(9)	119.0
C(3)-C(2)-H(2)	118.8	C(14)-C(9)-H(9)	119.0
C(1)-C(2)-H(2)	118.8	C(1)-C(10)-C(11)	121.2(7)
C(2)-C(3)-C(4)	120.9(7)	C(1)-C(10)-N(2)	131.9(7)
C(2)-C(3)-H(3)	119.5	C(11)-C(10)-N(2)	106.8(6)
C(4)-C(3)-H(3)	119.5	C(4)-C(11)-C(10)	122.2(7)
C(11)-C(4)-C(3)	116.7(7)	C(4)-C(11)-N(3)	130.4(7)
C(11)-C(4)-H(4)	121.6	C(10)-C(11)-N(3)	107.4(7)
C(3)-C(4)-H(4)	121.6	N(1)-C(12)-N(3)	126.4(7)
N(1)-C(12)-N(2)	126.8(7)	O(4)-C(15)-C(16)	124.2(8)
N(3)-C(12)-N(2)	106.8(6)	N(2)-C(15)-C(16)	117.7(7)
C(6)-C(13)-C(14)	120.5(6)	C(15)-C(16)-H(16A)	109.3

C(6)-C(13)-C(5)	119.6(6)	C(15)-C(16)-H(16B)	109.5
C(14)-C(13)-C(5)	119.9(7)	H(16A)-C(16)-H(16B)	109.5
N(1)-C(14)-C(9)	118.3(6)	C(15)-C(16)-H(16C)	109.6
N(1)-C(14)-C(13)	123.7(6)	H(16A)-C(16)-H(16C)	109.5
C(9)-C(14)-C(13)	118.0(7)	H(16B)-C(16)-H(16C)	109.5
O(4)-C(15)-N(2)	118.1(7)		

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for GKK/006/070. The anisotropic displacement factor exponent takes the form:
$-2\pi^2[h^2 a^{*2} U_{11} + ... + 2 h k a^* b^* U_{12}]$

	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
O(1)	43(3)	12(3)	43(4)	6(2)	14(3)	2(2)
O(2)	47(3)	21(3)	44(4)	-2(3)	14(3)	4(3)
O(3)	44(3)	32(3)	39(4)	7(3)	13(3)	-5(3)
O(4)	50(4)	25(3)	51(4)	1(3)	23(3)	8(3)
N(1)	33(4)	14(3)	33(4)	4(3)	3(3)	-3(3)
N(2)	34(4)	18(3)	29(4)	-1(3)	8(3)	3(3)
N(3)	32(3)	12(3)	28(4)	4(3)	8(3)	0(3)
N(4)	30(4)	25(4)	34(5)	4(3)	4(3)	-1(3)
C(1)	31(4)	31(5)	27(5)	-1(4)	1(4)	0(4)
C(2)	38(5)	36(5)	32(5)	3(4)	9(4)	-7(4)
C(3)	38(5)	28(5)	34(5)	6(4)	8(4)	-3(4)
C(4)	35(4)	19(4)	36(5)	2(4)	2(4)	1(3)
C(5)	28(4)	20(4)	29(5)	4(4)	0(4)	5(3)
C(6)	29(4)	17(4)	23(5)	-1(3)	0(4)	1(3)
C(7)	25(4)	29(5)	22(5)	-2(3)	-2(3)	1(3)
C(8)	35(4)	16(4)	31(5)	2(3)	5(4)	-1(3)
C(9)	37(5)	13(4)	35(5)	1(4)	2(4)	0(3)
C(10)	27(4)	24(4)	28(5)	4(3)	0(4)	-1(3)
C(11)	26(4)	26(4)	35(5)	1(4)	1(4)	0(3)
C(12)	30(4)	18(3)	28(5)	-1(4)	0(4)	3(4)
C(13)	28(4)	14(4)	27(5)	-1(3)	0(4)	-2(3)
C(14)	25(4)	24(4)	19(5)	-1(3)	-1(4)	2(3)
C(15)	42(5)	21(4)	33(5)	1(4)	-2(4)	7(4)
C(16)	51(6)	17(4)	53(6)	-8(4)	17(5)	2(4)

Table 5. Hydrogen coordinates and isotropic displacement parameters for GKK/006/070.

	x	y	z	U(eq)
H(1)	-0.5027	0.4857	0.9677	0.035
H(2)	-0.6092	0.3374	0.9862	0.042
H(3)	-0.3880	0.2348	0.8501	0.040
H(4)	-0.0704	0.2759	0.6712	0.036
H(6)	0.6567	0.3931	0.3306	0.027
H(8)	0.8607	0.6450	0.2740	0.033
H(9)	0.5543	0.6858	0.4489	0.034
H(16A)	-0.0603	0.7529	0.8786	0.060
H(16B)	-0.0468	0.7235	0.7075	0.060
H(16C)	0.1833	0.6934	0.8268	0.060

Table 6. Torsion angles [°] for GKK/006/070.

C(10)-C(1)-C(2)-C(3)	0.6(13)	C(12)-N(3)-C(11)-C(10)	1.8(9)
C(1)-C(2)-C(3)-C(4)	-2.4(13)	C(5)-N(3)-C(11)-C(10)	-178.9(7)
C(2)-C(3)-C(4)-C(11)	3.9(12)	C(14)-N(1)-C(12)-N(3)	-0.8(11)
C(12)-N(3)-C(5)-O(1)	-178.8(7)	C(14)-N(1)-C(12)-N(2)	180.0(7)
C(11)-N(3)-C(5)-O(1)	2.0(12)	C(11)-N(3)-C(12)-N(1)	-179.7(7)
C(12)-N(3)-C(5)-C(13)	0.5(10)	C(5)-N(3)-C(12)-N(1)	0.9(12)
C(11)-N(3)-C(5)-C(13)	-178.7(7)	C(11)-N(3)-C(12)-N(2)	-0.4(8)
C(13)-C(6)-C(7)-C(8)	-1.4(11)	C(5)-N(3)-C(12)-N(2)	-179.7(6)
C(13)-C(6)-C(7)-N(4)	177.2(7)	C(10)-N(2)-C(12)-N(1)	178.1(7)
O(3)-N(4)-C(7)-C(6)	177.4(7)	C(15)-N(2)-C(12)-N(1)	-2.7(12)
O(2)-N(4)-C(7)-C(6)	-4.7(11)	C(10)-N(2)-C(12)-N(3)	-1.2(8)
O(3)-N(4)-C(7)-C(8)	-4.0(11)	C(15)-N(2)-C(12)-N(3)	178.0(7)
O(2)-N(4)-C(7)-C(8)	173.9(7)	C(7)-C(6)-C(13)-C(14)	-0.5(10)
C(6)-C(7)-C(8)-C(9)	2.1(12)	C(7)-C(6)-C(13)-C(5)	179.0(7)
N(4)-C(7)-C(8)-C(9)	-176.5(7)	O(1)-C(5)-C(13)-C(6)	-2.2(12)
C(7)-C(8)-C(9)-C(14)	-0.8(12)	N(3)-C(5)-C(13)-C(6)	178.6(6)
C(2)-C(1)-C(10)-C(11)	-0.6(12)	O(1)-C(5)-C(13)-C(14)	177.3(8)
C(2)-C(1)-C(10)-N(2)	-177.3(8)	N(3)-C(5)-C(13)-C(14)	-2.0(10)
C(12)-N(2)-C(10)-C(1)	179.5(8)	C(12)-N(1)-C(14)-C(9)	179.3(7)
C(15)-N(2)-C(10)-C(1)	0.2(13)	C(12)-N(1)-C(14)-C(13)	-0.9(11)
C(12)-N(2)-C(10)-C(11)	2.3(8)	C(8)-C(9)-C(14)-N(1)	178.9(7)
C(15)-N(2)-C(10)-C(11)	-176.9(7)	C(8)-C(9)-C(14)-C(13)	-0.9(11)
C(3)-C(4)-C(11)-C(10)	-3.9(12)	C(6)-C(13)-C(14)-N(1)	-178.2(7)
C(3)-C(4)-C(11)-N(3)	179.0(8)	C(5)-C(13)-C(14)-N(1)	2.3(12)
C(1)-C(10)-C(11)-C(4)	2.3(12)	C(6)-C(13)-C(14)-C(9)	1.6(11)
N(2)-C(10)-C(11)-C(4)	179.8(7)	C(5)-C(13)-C(14)-C(9)	-177.9(7)
C(1)-C(10)-C(11)-N(3)	180.0(7)	C(12)-N(2)-C(15)-O(4)	174.2(7)
N(2)-C(10)-C(11)-N(3)	-2.5(8)	C(10)-N(2)-C(15)-O(4)	-6.7(11)
C(12)-N(3)-C(11)-C(4)	179.2(8)	C(12)-N(2)-C(15)-C(16)	-6.3(11)
C(5)-N(3)-C(11)-C(4)	-1.5(13)	C(10)-N(2)-C(15)-C(16)	172.8(7)

Table 7. Hydrogen bonds for GKK/006/070[Å and °].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
C(1)-H(1)...O(3)#1	0.95	2.52	3.415(10)	156.7
C(1)-H(1)...O(4)	0.95	2.33	2.861(10)	114.4
C(4)-H(4)...O(1)	0.95	2.48	3.006(10)	114.9
C(9)-H(9)...O(1)#2	0.95	2.49	3.370(10)	154.0

Symmetry transformations used to generate equivalent atoms:
#1 x-2, y, z+1 #2 -x+1, y+1/2, -z+1

Appendices C: X-ray data for methyl (±)-*R*,*R*-1-(2-(4-nitrophenyl)propyl)-2-oxocyclopentane-1-carboxylate [(±)-*R*,*R*-57b]

Table 1. Crystal data and structure refinement for GKK/007/032BF2.

Empirical formula	C_{16} H_{19} N O_5	
Formula weight	305.32	
Crystal system	orthorhombic	
Space group	*Pbcn*	
Unit cell dimensions	*a* = 18.786(18) Å	α= 90°
	b = 11.569(11) Å	β= 90°
	c = 27.37(2) Å	γ= 90°
Volume	5948(9) $Å^3$	
Z, Z'	16, 2	
Density (calculated)	1.364 Mg/m^3	
Wavelength	0.71073 Å	
Temperature	100(2) K	
F(000)	2592	
Absorption coefficient	0.102 mm^{-1}	
Absorption correction	semi-empirical from equivalents	
Max. and min. transmission	0.997 and 0.963	
Theta range for data collection	1.488 to 18.847°	
Reflections collected	15872	
Independent reflections	2345 [R(int) = 0.1310]	
Data / restraints / parameters	2345 / 336 / 397	
wR(F^2 all data)	*wR*2 = 0.3068	
R(*F* obsd data)	*R*1 = 0.1089	
Goodness-of-fit on F^2	1.138	
Observed data [I > 2σ(I)]	1623	
Largest and mean shift / s.u.	0.000 and 0.000	
Largest diff. peak and hole	0.608 and -0.298 $e/Å^3$	

$wR2 = \{ \Sigma [w(F_o^2 - F_c^2)^2] / \Sigma [w(F_o^2)^2] \}^{1/2}$

$R1 = \Sigma ||F_o| - |F_c|| / \Sigma |F_o|$

Table 2. Atomic coordinates and equivalent isotropic displacement parameters GKK/007/032BF2. U(eq) is defined as one third of the trace of the orthogonalized tensor.

	x	y	z	U(eq)
O(1A)	0.1695(4)	0.1938(7)	0.2007(3)	0.052(2)
O(2A)	0.4587(5)	0.2486(8)	0.4471(3)	0.054(3)
O(3A)	0.4491(5)	0.4327(8)	0.4579(3)	0.057(3)
O(4A)	0.2100(4)	0.4012(7)	0.3294(3)	0.043(2)
O(5A)	0.2333(4)	0.2202(6)	0.3040(3)	0.039(2)
N(1A)	0.4459(5)	0.3475(10)	0.4320(4)	0.043(3)
C(1A)	0.2189(6)	0.3604(9)	0.2419(4)	0.030(2)
C(2A)	0.1604(7)	0.2886(11)	0.2188(4)	0.041(3)
C(3A)	0.0942(7)	0.3572(10)	0.2164(5)	0.052(4)
C(4A)	0.1102(6)	0.4714(10)	0.2410(5)	0.045(3)
C(5A)	0.1895(6)	0.4827(10)	0.2334(5)	0.046(3)
C(6A)	0.2913(6)	0.3361(11)	0.2182(5)	0.046(3)
C(7A)	0.3548(6)	0.4070(11)	0.2335(4)	0.043(3)
C(8A)	0.4164(6)	0.3879(11)	0.1999(4)	0.040(3)
C(9A)	0.3776(6)	0.3906(10)	0.2857(4)	0.031(3)
C(10A)	0.3909(5)	0.2784(10)	0.3047(4)	0.034(3)
C(11A)	0.4149(6)	0.2638(10)	0.3524(4)	0.032(3)
C(12A)	0.4255(6)	0.3614(9)	0.3801(4)	0.031(3)
C(13A)	0.4162(5)	0.4721(9)	0.3620(4)	0.028(3)
C(14A)	0.3926(6)	0.4819(10)	0.3153(4)	0.033(3)
C(15A)	0.2199(6)	0.3372(11)	0.2973(5)	0.032(3)
C(16A)	0.2374(6)	0.1847(10)	0.3538(4)	0.036(3)
O(1B)	0.3538(4)	0.5309(7)	0.5874(3)	0.050(2)
O(2B)	0.0426(4)	0.4542(7)	0.3661(3)	0.046(2)
O(3B)	0.0589(4)	0.2707(6)	0.3593(3)	0.038(2)
O(4B)	0.2976(4)	0.3076(7)	0.4755(3)	0.043(2)
O(5B)	0.2682(4)	0.4887(7)	0.4976(3)	0.042(2)
N(1B)	0.0601(5)	0.3611(9)	0.3830(4)	0.034(2)
C(1B)	0.2902(6)	0.3596(9)	0.5631(4)	0.032(2)
C(2B)	0.3555(6)	0.4302(11)	0.5794(4)	0.038(3)
C(3B)	0.4184(6)	0.3552(9)	0.5871(5)	0.041(3)
C(4B)	0.3946(6)	0.2339(10)	0.5673(5)	0.046(3)
C(5B)	0.3144(6)	0.2347(10)	0.5729(5)	0.041(3)
C(6B)	0.2248(6)	0.3978(11)	0.5893(5)	0.041(3)
C(7B)	0.1563(6)	0.3355(11)	0.5813(4)	0.039(3)
C(8B)	0.0994(6)	0.3709(10)	0.6182(4)	0.042(3)

C(9B)	0.1285(6)	0.3401(10)	0.5296(4)	0.035(3)
C(10B)	0.1066(6)	0.4465(10)	0.5094(4)	0.039(3)
C(11B)	0.0826(6)	0.4521(10)	0.4614(4)	0.032(3)
C(12B)	0.0801(6)	0.3539(10)	0.4342(4)	0.031(3)
C(13B)	0.1000(6)	0.2485(10)	0.4538(4)	0.036(3)
C(14B)	0.1217(6)	0.2435(11)	0.5009(4)	0.036(3)
C(15B)	0.2859(6)	0.3772(10)	0.5073(5)	0.030(3)
C(16B)	0.2607(7)	0.5171(11)	0.4466(4)	0.041(3)

Table 3. Bond lengths [Å] and angles [°] for GKK/007/032BF2.

O(1A)-C(2A)	1.216(14)	O(1B)-C(2B)	1.186(13)
O(2A)-N(1A)	1.240(12)	O(2B)-N(1B)	1.219(11)
O(3A)-N(1A)	1.215(12)	O(3B)-N(1B)	1.231(11)
O(4A)-C(15A)	1.166(13)	O(4B)-C(15B)	1.206(12)
O(5A)-C(15A)	1.389(14)	O(5B)-C(15B)	1.359(13)
O(5A)-C(16A)	1.427(13)	O(5B)-C(16B)	1.440(13)
N(1A)-C(12A)	1.481(16)	N(1B)-C(12B)	1.453(15)
C(1A)-C(2A)	1.516(17)	C(1B)-C(6B)	1.490(16)
C(1A)-C(5A)	1.537(15)	C(1B)-C(2B)	1.539(16)
C(1A)-C(6A)	1.533(16)	C(1B)-C(5B)	1.537(15)
C(1A)-C(15A)	1.538(17)	C(1B)-C(15B)	1.544(17)
C(2A)-C(3A)	1.477(17)	C(2B)-C(3B)	1.480(16)
C(3A)-C(4A)	1.513(16)	C(3B)-C(4B)	1.569(16)
C(3A)-H(3A1)	0.9900	C(3B)-H(3B1)	0.9900
C(3A)-H(3A2)	0.9900	C(3B)-H(3B2)	0.9900
C(4A)-C(5A)	1.510(16)	C(4B)-C(5B)	1.515(16)
C(4A)-H(4A1)	0.9900	C(4B)-H(4B1)	0.9900
C(4A)-H(4A2)	0.9900	C(4B)-H(4B2)	0.9900
C(5A)-H(5A1)	0.9900	C(5B)-H(5B1)	0.9900
C(5A)-H(5A2)	0.9900	C(5B)-H(5B2)	0.9900
C(6A)-C(7A)	1.506(17)	C(6B)-C(7B)	1.491(16)
C(6A)-H(6A1)	0.9900	C(6B)-H(6B1)	0.9900
C(6A)-H(6A2)	0.9900	C(6B)-H(6B2)	0.9900
C(7A)-C(8A)	1.496(16)	C(7B)-C(9B)	1.509(16)
C(7A)-C(9A)	1.503(16)	C(7B)-C(8B)	1.526(16)
C(7A)-H(7A)	1.0000	C(7B)-H(7B)	1.0000
C(8A)-H(8A1)	0.9800	C(8B)-H(8B1)	0.9800
C(8A)-H(8A2)	0.9800	C(8B)-H(8B2)	0.9800
C(8A)-H(8A3)	0.9800	C(8B)-H(8B3)	0.9800
C(9A)-C(14A)	1.362(15)	C(9B)-C(14B)	1.372(16)
C(9A)-C(10A)	1.421(16)	C(9B)-C(10B)	1.411(16)
C(10A)-C(11A)	1.392(15)	C(10B)-C(11B)	1.391(16)
C(10A)-H(10A)	0.9500	C(10B)-H(10B)	0.9500
C(11A)-C(12A)	1.373(15)	C(11B)-C(12B)	1.358(15)
C(11A)-H(11A)	0.9500	C(11B)-H(11B)	0.9500
C(12A)-C(13A)	1.384(15)	C(12B)-C(13B)	1.383(15)
C(13A)-C(14A)	1.357(15)	C(13B)-C(14B)	1.354(15)
C(13A)-H(13A)	0.9500	C(13B)-H(13B)	0.9500
C(14A)-H(14A)	0.9500	C(14B)-H(14B)	0.9500
C(16A)-H(16A)	0.9800	C(16B)-H(16D)	0.9800
C(16A)-H(16B)	0.9800	C(16B)-H(16E)	0.9800
C(16A)-H(16C)	0.9800	C(16B)-H(16F)	0.9800

C(15A)-O(5A)-C(16A)	114.7(9)	C(7A)-C(8A)-H(8A2)	109.3
O(3A)-N(1A)-O(2A)	123.0(11)	H(8A1)-C(8A)-H(8A2)	109.5
O(3A)-N(1A)-C(12A)	118.9(11)	C(7A)-C(8A)-H(8A3)	109.1
O(2A)-N(1A)-C(12A)	118.0(10)	H(8A1)-C(8A)-H(8A3)	109.5
C(2A)-C(1A)-C(5A)	100.4(9)	H(8A2)-C(8A)-H(8A3)	109.5
C(2A)-C(1A)-C(6A)	111.6(10)	C(14A)-C(9A)-C(10A)	117.0(11)
C(5A)-C(1A)-C(6A)	115.0(10)	C(14A)-C(9A)-C(7A)	121.8(11)
C(2A)-C(1A)-C(15A)	108.9(9)	C(10A)-C(9A)-C(7A)	121.0(11)
C(5A)-C(1A)-C(15A)	108.3(10)	C(11A)-C(10A)-C(9A)	120.8(11)
C(6A)-C(1A)-C(15A)	111.9(9)	C(11A)-C(10A)-H(10A)	119.6
O(1A)-C(2A)-C(3A)	125.8(12)	C(9A)-C(10A)-H(10A)	119.6
O(1A)-C(2A)-C(1A)	124.2(11)	C(12A)-C(11A)-C(10A)	117.7(11)
C(3A)-C(2A)-C(1A)	109.6(10)	C(12A)-C(11A)-H(11A)	121.2
C(2A)-C(3A)-C(4A)	106.4(10)	C(10A)-C(11A)-H(11A)	121.2
C(2A)-C(3A)-H(3A1)	110.5	C(11A)-C(12A)-C(13A)	123.1(11)
C(4A)-C(3A)-H(3A1)	110.5	C(11A)-C(12A)-N(1A)	118.5(10)
C(2A)-C(3A)-H(3A2)	110.5	C(13A)-C(12A)-N(1A)	118.4(10)
C(4A)-C(3A)-H(3A2)	110.5	C(14A)-C(13A)-C(12A)	117.1(11)
H(3A1)-C(3A)-H(3A2)	108.6	C(14A)-C(13A)-H(13A)	121.5
C(5A)-C(4A)-C(3A)	102.2(10)	C(12A)-C(13A)-H(13A)	121.5
C(5A)-C(4A)-H(4A1)	111.3	C(13A)-C(14A)-C(9A)	124.3(11)
C(3A)-C(4A)-H(4A1)	111.3	C(13A)-C(14A)-H(14A)	117.9
C(5A)-C(4A)-H(4A2)	111.3	C(9A)-C(14A)-H(14A)	117.9
C(3A)-C(4A)-H(4A2)	111.3	O(4A)-C(15A)-O(5A)	123.2(11)
H(4A1)-C(4A)-H(4A2)	109.2	O(4A)-C(15A)-C(1A)	129.1(11)
C(4A)-C(5A)-C(1A)	104.7(9)	O(5A)-C(15A)-C(1A)	107.6(10)
C(4A)-C(5A)-H(5A1)	110.8	O(5A)-C(16A)-H(16A)	109.7
C(1A)-C(5A)-H(5A1)	110.8	O(5A)-C(16A)-H(16B)	109.2
C(4A)-C(5A)-H(5A2)	110.8	H(16A)-C(16A)-H(16B)	109.5
C(1A)-C(5A)-H(5A2)	110.8	O(5A)-C(16A)-H(16C)	109.5
H(5A1)-C(5A)-H(5A2)	108.9	H(16A)-C(16A)-H(16C)	109.5
C(7A)-C(6A)-C(1A)	119.0(10)	H(16B)-C(16A)-H(16C)	109.5
C(7A)-C(6A)-H(6A1)	107.6	C(15B)-O(5B)-C(16B)	115.5(9)
C(1A)-C(6A)-H(6A1)	107.6	O(2B)-N(1B)-O(3B)	123.0(10)
C(7A)-C(6A)-H(6A2)	107.6	O(2B)-N(1B)-C(12B)	119.2(10)
C(1A)-C(6A)-H(6A2)	107.6	O(3B)-N(1B)-C(12B)	117.8(9)
H(6A1)-C(6A)-H(6A2)	107.0	C(6B)-C(1B)-C(2B)	111.2(10)
C(8A)-C(7A)-C(6A)	111.2(10)	C(6B)-C(1B)-C(5B)	116.0(10)
C(8A)-C(7A)-C(9A)	110.2(9)	C(2B)-C(1B)-C(5B)	102.3(9)
C(6A)-C(7A)-C(9A)	114.9(10)	C(6B)-C(1B)-C(15B)	113.1(10)
C(8A)-C(7A)-H(7A)	106.7	C(2B)-C(1B)-C(15B)	105.0(9)
C(6A)-C(7A)-H(7A)	106.7	C(5B)-C(1B)-C(15B)	108.2(10)
C(9A)-C(7A)-H(7A)	106.7	O(1B)-C(2B)-C(3B)	124.8(11)
C(7A)-C(8A)-H(8A1)	110.1	O(1B)-C(2B)-C(1B)	123.6(11)

C(3B)-C(2B)-C(1B)	111.5(10)	C(7B)-C(8B)-H(8B2)	109.4
C(2B)-C(3B)-C(4B)	104.4(9)	H(8B1)-C(8B)-H(8B2)	109.5
C(2B)-C(3B)-H(3B1)	110.9	C(7B)-C(8B)-H(8B3)	109.7
C(4B)-C(3B)-H(3B1)	110.9	H(8B1)-C(8B)-H(8B3)	109.5
C(2B)-C(3B)-H(3B2)	110.9	H(8B2)-C(8B)-H(8B3)	109.5
C(4B)-C(3B)-H(3B2)	110.9	C(14B)-C(9B)-C(10B)	117.4(11)
H(3B1)-C(3B)-H(3B2)	108.9	C(14B)-C(9B)-C(7B)	122.7(11)
C(5B)-C(4B)-C(3B)	104.0(9)	C(10B)-C(9B)-C(7B)	119.9(11)
C(5B)-C(4B)-H(4B1)	111.0	C(11B)-C(10B)-C(9B)	120.3(11)
C(3B)-C(4B)-H(4B1)	111.0	C(11B)-C(10B)-H(10B)	119.8
C(5B)-C(4B)-H(4B2)	111.0	C(9B)-C(10B)-H(10B)	119.8
C(3B)-C(4B)-H(4B2)	111.0	C(12B)-C(11B)-C(10B)	119.3(11)
H(4B1)-C(4B)-H(4B2)	109.0	C(12B)-C(11B)-H(11B)	120.3
C(4B)-C(5B)-C(1B)	106.4(9)	C(10B)-C(11B)-H(11B)	120.3
C(4B)-C(5B)-H(5B1)	110.5	C(11B)-C(12B)-C(13B)	121.1(11)
C(1B)-C(5B)-H(5B1)	110.5	C(11B)-C(12B)-N(1B)	119.3(10)
C(4B)-C(5B)-H(5B2)	110.5	C(13B)-C(12B)-N(1B)	119.6(10)
C(1B)-C(5B)-H(5B2)	110.5	C(14B)-C(13B)-C(12B)	119.2(11)
H(5B1)-C(5B)-H(5B2)	108.6	C(14B)-C(13B)-H(13B)	120.4
C(7B)-C(6B)-C(1B)	119.9(10)	C(12B)-C(13B)-H(13B)	120.4
C(7B)-C(6B)-H(6B1)	107.3	C(13B)-C(14B)-C(9B)	122.5(12)
C(1B)-C(6B)-H(6B1)	107.3	C(13B)-C(14B)-H(14B)	118.7
C(7B)-C(6B)-H(6B2)	107.3	C(9B)-C(14B)-H(14B)	118.7
C(1B)-C(6B)-H(6B2)	107.3	O(4B)-C(15B)-O(5B)	122.5(11)
H(6B1)-C(6B)-H(6B2)	106.9	O(4B)-C(15B)-C(1B)	128.0(11)
C(6B)-C(7B)-C(9B)	114.7(10)	O(5B)-C(15B)-C(1B)	109.4(10)
C(6B)-C(7B)-C(8B)	112.2(10)	O(5B)-C(16B)-H(16D)	109.5
C(9B)-C(7B)-C(8B)	111.7(10)	O(5B)-C(16B)-H(16E)	109.4
C(6B)-C(7B)-H(7B)	105.8	H(16D)-C(16B)-H(16E)	109.5
C(9B)-C(7B)-H(7B)	105.8	O(5B)-C(16B)-H(16F)	109.6
C(8B)-C(7B)-H(7B)	105.8	H(16D)-C(16B)-H(16F)	109.5
C(7B)-C(8B)-H(8B1)	109.2	H(16E)-C(16B)-H(16F)	109.5

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for GKK/007/032BF2.
The anisotropic displacement factor exponent takes the form:
$-2\pi^2[h^2 a^{*2} U_{11} + ... + 2 h k a^* b^* U_{12}]$

	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
O(1A)	55(5)	38(5)	62(6)	-2(4)	-6(5)	-2(4)
O(2A)	60(6)	53(5)	48(5)	11(4)	-7(5)	-3(5)
O(3A)	58(6)	62(6)	53(5)	-16(4)	4(5)	-15(5)
O(4A)	40(5)	41(5)	50(5)	-9(4)	-3(4)	0(4)
O(5A)	57(5)	25(4)	37(4)	2(3)	-5(4)	-1(4)
N(1A)	34(6)	50(6)	44(5)	1(4)	0(4)	-10(5)
C(1A)	28(4)	21(5)	42(5)	2(4)	-1(4)	-3(4)
C(2A)	42(5)	34(5)	47(7)	3(5)	-1(5)	-8(4)
C(3A)	39(6)	41(6)	75(9)	-3(6)	-2(5)	-4(5)
C(4A)	50(6)	34(6)	52(8)	12(5)	-5(5)	5(5)
C(5A)	47(6)	29(5)	62(8)	3(5)	-2(5)	1(4)
C(6A)	32(5)	55(7)	52(7)	-1(6)	0(4)	-1(4)
C(7A)	36(5)	49(7)	43(5)	-1(5)	0(4)	1(5)
C(8A)	23(6)	65(9)	33(6)	-1(6)	-6(5)	-4(5)
C(9A)	19(6)	34(5)	40(5)	-5(4)	4(4)	7(5)
C(10A)	20(6)	32(5)	51(5)	-9(4)	-2(5)	4(5)
C(11A)	26(7)	21(5)	51(5)	0(4)	-3(5)	4(5)
C(12A)	31(7)	23(5)	38(5)	0(4)	1(4)	-6(5)
C(13A)	24(6)	21(5)	40(5)	-7(4)	13(5)	-1(5)
C(14A)	33(7)	24(5)	41(5)	-2(4)	7(5)	1(5)
C(15A)	16(6)	31(5)	49(5)	0(4)	-4(4)	-5(4)
C(16A)	34(7)	36(7)	38(6)	4(5)	-2(5)	7(6)
O(1B)	62(6)	22(4)	64(6)	8(4)	-12(5)	-3(4)
O(2B)	54(6)	32(5)	53(5)	1(4)	-6(4)	8(4)
O(3B)	38(5)	24(4)	53(5)	-5(4)	-7(4)	1(4)
O(4B)	44(5)	33(5)	53(5)	-7(4)	-5(4)	-2(4)
O(5B)	54(5)	30(4)	42(4)	8(3)	-3(4)	-2(4)
N(1B)	32(6)	28(5)	41(5)	-3(4)	1(4)	-1(4)
C(1B)	31(4)	17(5)	48(5)	0(4)	-1(4)	-2(4)
C(2B)	41(5)	20(5)	55(7)	4(5)	-9(5)	-2(4)
C(3B)	40(5)	26(5)	57(8)	5(5)	-13(5)	0(4)
C(4B)	50(6)	25(5)	63(9)	1(5)	-6(6)	0(4)
C(5B)	49(5)	25(5)	50(7)	-1(5)	1(5)	-3(4)
C(6B)	35(5)	36(7)	53(7)	3(5)	3(4)	4(4)
C(7B)	41(5)	35(6)	41(5)	7(5)	4(4)	-3(4)

C(8B)	38(6)	34(8)	53(7)	-3(6)	9(5)	-7(6)
C(9B)	24(6)	37(5)	44(5)	2(4)	8(4)	-3(5)
C(10B)	47(8)	29(5)	42(5)	-8(4)	-3(5)	-1(5)
C(11B)	27(7)	29(5)	40(5)	-6(4)	5(5)	3(5)
C(12B)	23(6)	25(5)	43(5)	-5(4)	-2(4)	-1(5)
C(13B)	42(8)	25(5)	41(5)	-4(4)	1(5)	0(5)
C(14B)	30(7)	33(5)	45(5)	2(4)	1(5)	-1(5)
C(15B)	16(6)	25(5)	50(5)	-4(4)	-1(4)	-13(4)
C(16B)	48(8)	34(7)	41(5)	10(5)	-2(5)	-5(6)

Table 5. Hydrogen coordinates and isotropic displacement parameters for GKK/007/032BF2.

	x	y	z	U(eq)
H(3A1)	0.0550	0.3168	0.2336	0.062
H(3A2)	0.0799	0.3697	0.1820	0.062
H(4A1)	0.0841	0.5357	0.2252	0.054
H(4A2)	0.0981	0.4692	0.2762	0.054
H(5A1)	0.2103	0.5381	0.2570	0.055
H(5A2)	0.2003	0.5095	0.1998	0.055
H(6A1)	0.3030	0.2539	0.2242	0.056
H(6A2)	0.2856	0.3454	0.1825	0.056
H(7A)	0.3407	0.4900	0.2300	0.051
H(8A1)	0.4337	0.3083	0.2030	0.060
H(8A2)	0.4548	0.4418	0.2083	0.060
H(8A3)	0.4010	0.4019	0.1662	0.060
H(10A)	0.3832	0.2125	0.2847	0.041
H(11A)	0.4237	0.1890	0.3654	0.039
H(13A)	0.4260	0.5382	0.3814	0.034
H(14A)	0.3860	0.5575	0.3025	0.039
H(16A)	0.2741	0.2296	0.3708	0.054
H(16B)	0.2495	0.1024	0.3552	0.054
H(16C)	0.1913	0.1973	0.3697	0.054
H(3B1)	0.4308	0.3509	0.6222	0.049
H(3B2)	0.4600	0.3846	0.5687	0.049
H(4B1)	0.4084	0.2242	0.5327	0.055
H(4B2)	0.4162	0.1708	0.5868	0.055
H(5B1)	0.3007	0.2106	0.6063	0.049
H(5B2)	0.2922	0.1812	0.5492	0.049
H(6B1)	0.2352	0.3950	0.6247	0.050
H(6B2)	0.2167	0.4800	0.5808	0.050
H(7B)	0.1665	0.2522	0.5880	0.047
H(8B1)	0.1160	0.3525	0.6513	0.063
H(8B2)	0.0553	0.3283	0.6115	0.063
H(8B3)	0.0904	0.4541	0.6157	0.063
H(10B)	0.1083	0.5147	0.5287	0.047
H(11B)	0.0682	0.5238	0.4477	0.039
H(13B)	0.0985	0.1805	0.4344	0.043
H(14B)	0.1325	0.1702	0.5147	0.043
H(16D)	0.3067	0.5078	0.4302	0.062
H(16E)	0.2447	0.5974	0.4435	0.062
H(16F)	0.2256	0.4656	0.4315	0.062

Table 6. Torsion angles [°] for GKK/007/032BF2.

C(5A)-C(1A)-C(2A)-O(1A)	152.0(12)
C(6A)-C(1A)-C(2A)-O(1A)	29.6(16)
C(15A)-C(1A)-C(2A)-O(1A)	-94.4(14)
C(5A)-C(1A)-C(2A)-C(3A)	-21.0(12)
C(6A)-C(1A)-C(2A)-C(3A)	-143.4(11)
C(15A)-C(1A)-C(2A)-C(3A)	92.6(12)
O(1A)-C(2A)-C(3A)-C(4A)	-176.1(12)
C(1A)-C(2A)-C(3A)-C(4A)	-3.3(14)
C(2A)-C(3A)-C(4A)-C(5A)	26.8(13)
C(3A)-C(4A)-C(5A)-C(1A)	-40.5(13)
C(2A)-C(1A)-C(5A)-C(4A)	37.8(12)
C(6A)-C(1A)-C(5A)-C(4A)	157.7(10)
C(15A)-C(1A)-C(5A)-C(4A)	-76.3(12)
C(2A)-C(1A)-C(6A)-C(7A)	174.8(11)
C(5A)-C(1A)-C(6A)-C(7A)	61.3(15)
C(15A)-C(1A)-C(6A)-C(7A)	-62.8(14)
C(1A)-C(6A)-C(7A)-C(8A)	-168.6(10)
C(1A)-C(6A)-C(7A)-C(9A)	65.5(15)
C(8A)-C(7A)-C(9A)-C(14A)	100.2(13)
C(6A)-C(7A)-C(9A)-C(14A)	-133.3(12)
C(8A)-C(7A)-C(9A)-C(10A)	-74.0(14)
C(6A)-C(7A)-C(9A)-C(10A)	52.5(15)
C(14A)-C(9A)-C(10A)-C(11A)	2.8(15)
C(7A)-C(9A)-C(10A)-C(11A)	177.3(10)
C(9A)-C(10A)-C(11A)-C(12A)	-0.2(16)
C(10A)-C(11A)-C(12A)-C(13A)	-2.8(16)
C(10A)-C(11A)-C(12A)-N(1A)	175.5(9)
O(3A)-N(1A)-C(12A)-C(11A)	-173.5(10)
O(2A)-N(1A)-C(12A)-C(11A)	6.2(15)
O(3A)-N(1A)-C(12A)-C(13A)	5.0(15)
O(2A)-N(1A)-C(12A)-C(13A)	-175.4(10)
C(11A)-C(12A)-C(13A)-C(14A)	2.9(16)
N(1A)-C(12A)-C(13A)-C(14A)	-175.4(9)
C(12A)-C(13A)-C(14A)-C(9A)	0.0(16)
C(10A)-C(9A)-C(14A)-C(13A)	-2.8(16)
C(7A)-C(9A)-C(14A)-C(13A)	-177.2(10)
C(16A)-O(5A)-C(15A)-O(4A)	-2.8(15)
C(16A)-O(5A)-C(15A)-C(1A)	178.8(9)
C(2A)-C(1A)-C(15A)-O(4A)	-117.9(13)
C(5A)-C(1A)-C(15A)-O(4A)	-9.5(16)
C(6A)-C(1A)-C(15A)-O(4A)	118.3(13)
C(2A)-C(1A)-C(15A)-O(5A)	60.4(11)

C(5A)-C(1A)-C(15A)-O(5A)	168.7(8)
C(6A)-C(1A)-C(15A)-O(5A)	-63.4(11)
C(6B)-C(1B)-C(2B)-O(1B)	-39.3(16)
C(5B)-C(1B)-C(2B)-O(1B)	-163.8(12)
C(15B)-C(1B)-C(2B)-O(1B)	83.3(14)
C(6B)-C(1B)-C(2B)-C(3B)	136.8(11)
C(5B)-C(1B)-C(2B)-C(3B)	12.3(13)
C(15B)-C(1B)-C(2B)-C(3B)	-100.6(11)
O(1B)-C(2B)-C(3B)-C(4B)	-175.6(12)
C(1B)-C(2B)-C(3B)-C(4B)	8.4(14)
C(2B)-C(3B)-C(4B)-C(5B)	-26.2(13)
C(3B)-C(4B)-C(5B)-C(1B)	34.7(13)
C(6B)-C(1B)-C(5B)-C(4B)	-150.2(11)
C(2B)-C(1B)-C(5B)-C(4B)	-29.0(12)
C(15B)-C(1B)-C(5B)-C(4B)	81.5(11)
C(2B)-C(1B)-C(6B)-C(7B)	-176.0(10)
C(5B)-C(1B)-C(6B)-C(7B)	-59.7(15)
C(15B)-C(1B)-C(6B)-C(7B)	66.1(14)
C(1B)-C(6B)-C(7B)-C(9B)	-62.5(15)
C(1B)-C(6B)-C(7B)-C(8B)	168.6(10)
C(6B)-C(7B)-C(9B)-C(14B)	115.8(12)
C(8B)-C(7B)-C(9B)-C(14B)	-115.1(12)
C(6B)-C(7B)-C(9B)-C(10B)	-65.9(14)
C(8B)-C(7B)-C(9B)-C(10B)	63.2(14)
C(14B)-C(9B)-C(10B)-C(11B)	-3.2(17)
C(7B)-C(9B)-C(10B)-C(11B)	178.4(10)
C(9B)-C(10B)-C(11B)-C(12B)	0.4(17)
C(10B)-C(11B)-C(12B)-C(13B)	0.9(17)
C(10B)-C(11B)-C(12B)-N(1B)	-175.4(10)
O(2B)-N(1B)-C(12B)-C(11B)	-3.7(15)
O(3B)-N(1B)-C(12B)-C(11B)	179.4(10)
O(2B)-N(1B)-C(12B)-C(13B)	179.9(10)
O(3B)-N(1B)-C(12B)-C(13B)	3.0(15)
C(11B)-C(12B)-C(13B)-C(14B)	0.6(17)
N(1B)-C(12B)-C(13B)-C(14B)	177.0(10)
C(12B)-C(13B)-C(14B)-C(9B)	-3.7(18)
C(10B)-C(9B)-C(14B)-C(13B)	4.9(17)
C(7B)-C(9B)-C(14B)-C(13B)	-176.7(11)
C(16B)-O(5B)-C(15B)-O(4B)	3.0(15)
C(16B)-O(5B)-C(15B)-C(1B)	-178.7(9)
C(6B)-C(1B)-C(15B)-O(4B)	-128.7(12)
C(2B)-C(1B)-C(15B)-O(4B)	109.9(13)
C(5B)-C(1B)-C(15B)-O(4B)	1.2(16)
C(6B)-C(1B)-C(15B)-O(5B)	53.1(12)
C(2B)-C(1B)-C(15B)-O(5B)	-68.3(11)

Table 7. Hydrogen bonds for GKK/007/032BF2 [Å and °].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
C(16A)-H(16B)...O(4A)#1	0.98	2.55	3.490(14)	161.2
C(16A)-H(16C)...O(3B)	0.98	2.64	3.500(14)	146.2
C(11B)-H(11B)...O(2A)#2	0.95	2.65	3.538(15)	156.1

Symmetry transformations used to generate equivalent atoms:

#1 -x+1/2, y-1/2, z #2 -x+1/2, y+1/2, z

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