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Synthesis of Highly Functionalized Spirobutenolides via Nitroalkane Mediated Ring Contraction of 2-Oxobenzo[*h*]chromenes through Denitration

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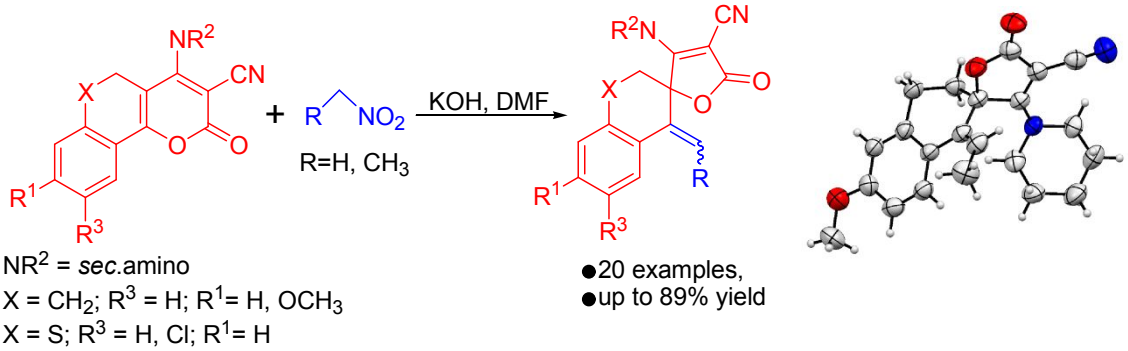
ABSTRACT



A facile synthesis of highly functionalized spirobutenolides was carried out by nitroalkane carbanion induced ring opening and relactonization via denitration reaction of 2-oxo-5,6-dihydro-2*H*-benzo[*h*]chromene-3-carbonitriles and 2-oxo-2,5-dihydrothiochromeno[4,3-b]pyran-3-carbonitriles. However, when nitroethane was used as a nucleophile source in lieu of nitromethane, a mixture of (*E*)- and (*Z*)-isomer of corresponding spirobutenolides were obtained in different ratio. The structure and geometry of the product was confirmed by single crystal X-ray diffraction. The isolated (*E*)- and (*Z*)-butenolides on treatment with sodium ethoxide in DMF at room temperature provided highly substituted trienes via allylic ring opening followed by decarboxylation.

INTRODUCTION

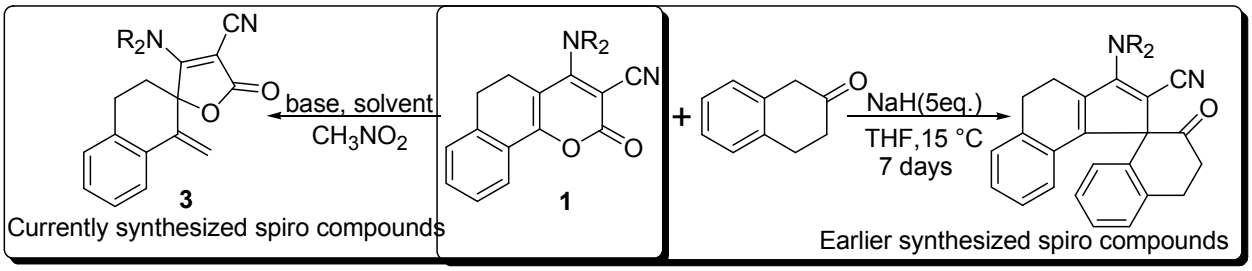
Butenolides are five membered lactones, which occur as a structural subunit in wide range of natural products of biological importance.[1,2] Butenolides based compounds exhibit diverse biological activities as anti-inflammatory,[3] anticancer,[4] antimicrobial,[5] antifungal[6] and anti-HIV-1.[7] There importance is not only limited to their biodynamic

properties, but they are also useful versatile building blocks for assembling different isolated and fused heterocycles of high biological relevance.[8-11]

Simple spirobutenolides are prepared by addition of lithium β-lithiopropionate to carbonyl compounds followed by lactonization.[12] Light mediated reaction of secondary alcohols with acetylenic esters provided spiro-γ-butenolides.[13] Three-component condensation reaction of primary amines, dialkyl acetylenedicarboxylates and 1,3-dimethylalloxan afforded oxaspirobutanolides.[14] N. Sucman et al. prepared butenolide functionalized spirooxindoles by reaction of N-substituted isatin with dimethyl acetylenedicarboxylate in presence of triphenylphosphine.[15] A gold catalyzed approach has been established for constructing spirobutenolides from (*Z*)-enynols having cyclic substituent at the C-1 position.[16] Hejmanowska et al. developed a novel approach to construct spirobutanolides via trienamine-mediated [4+2]-cycloaddition reaction of (*E*)-3-alkylidene-5-arylfuran-2(3*H*)-ones and 2,4-dienals.[17] Langer and Albrecht have reported the synthesis of spirobutenolides through ring closing metathesis of vinylacrylates using Grubbs' generation I catalyst and catalytic amounts of $Ti(O\text{-}i\text{-}Pr)_4$.[18] Spirobutenolides could also achieved by condensation of α-hydroxy α-acetyl lactones or N-benzyl lactams with

dimethyl malonate.[19] Another approach was employed by M. Piltan to access spiro-butenolide-indenetriones by heating of indeno[1,2-b]pyrrole-2,3-dicarboxylate derivatives in presence of catalytic amount of sulfuric acid in acetic acid.[20] Recently, Ram et al have reported the synthesis of various spiro compounds by ring transformation of 5,6-dihydro-2-oxo-2*H*-benzo[*h*]chromene-3-carbonitriles with 2-tetralone in the presence of NaH in THF by stirring for 7 days at 15 °C[21] (Scheme 1).

Scheme 1. Synthesis of Spiro Compounds from 2*H*-Benzo[*h*]chromene



Nitroalkanes act as valuable carbanion source and α proton has higher acidity due to strong electron withdrawing nature of nitro group. It was proposed that same as enolate, nitroalkane also stabilized as nitronate anion but oxygen of later compound is not reactive as enolate ion. As per earlier reports, nitronate anions react with different

electrophiles such as aldehydes, ketones, haloalkanes and α,β-unsaturated compounds resulting carbon-carbon bond formation.[22-24]

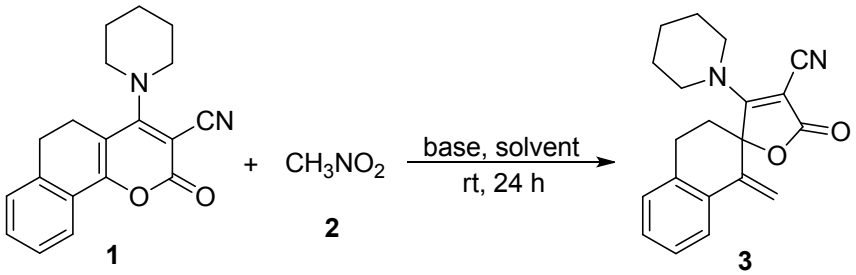
Herein, we have used α,β- and γ,δ-unsaturated compounds to study the effect of nitronate anion. In our study, we have successfully achieved functionalized spirobutenolides through ring opening and ring contraction followed by denitration. Furthermore, the butenolides reacting with sodium ethoxide and produced functionalized trienes, which can act as useful precursor for the construction of diverse class of compounds.

RESULTS AND DISCUSSION

The required precursors, 4-substituted-2-oxo-5,6-dihydro-2*H*-benzo[*h*]chromene-3-carbonitriles **1** were prepared in two steps. The reaction of ethyl 2-cyano-3,3 bis(methylthio)acrylate with 1-tetralone/6-methoxy-1-tetralone in DMSO under basic conditions provided functionalized 4-(methylthio)-2-oxo-5,6-dihydro-2*H*-benzo[*h*]chromene-3-carbonitriles, which underwent amination with various secondary amine in ethanol to afford 4-*sec.*amino-2-oxo-5,6-dihydro-2*H*-benzo[*h*]chromene-3-carbonitriles **1**.[25]

In order to optimize the conditions, a reaction of 2-oxo-4-(piperidin-1-yl)-5,6-dihydro-2*H* benzo[*h*]chromene-3-carbonitrile **1** and nitromethane **2** was selected as model reaction. Initially, we examined potassium hydroxide in THF at room temperature and 60 °C (Table 1, Entries 1 and 2), sodium hydride and lithium hydroxide in THF (Table 1, Entries 3 and 4) and a complex

Table 1. Optimization of Reaction Conditions[a]

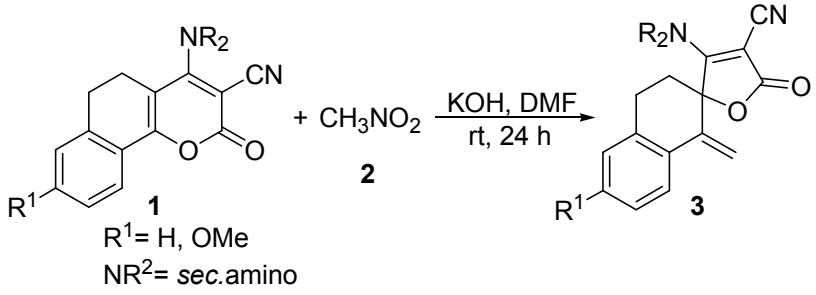


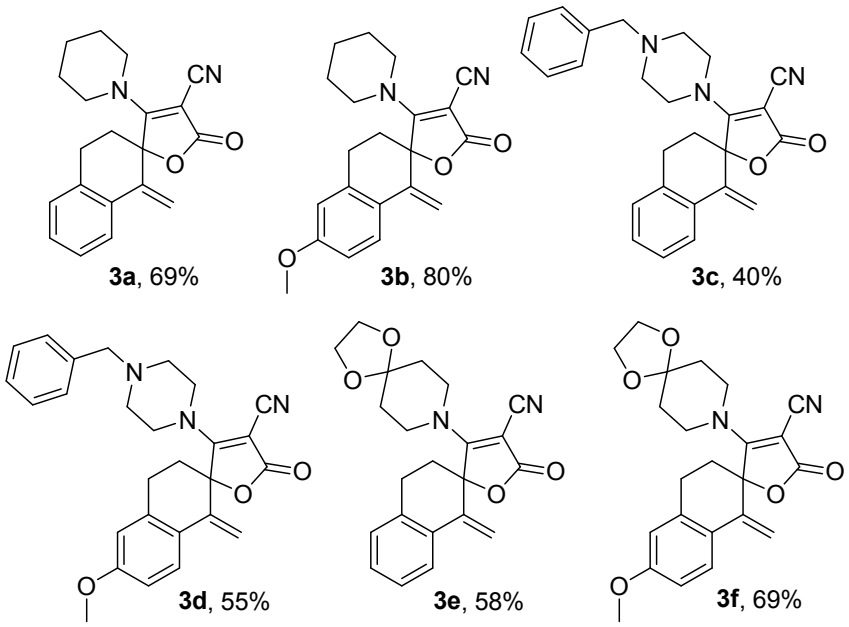
Entry	Base	Solvent	Yields[d] (%)	Entry	Base	Solvent	Yields[d] (%)
1	KOH	THF	-[e]	11	CH_3COONa	DMSO	trace
2[b]	KOH	THF	-[e]	12	K_2CO_3	DMSO	19
3	NaH	THF	-[e]	13	NaOEt	EtOH	-[e]
4	LiOH	THF	-[e]	14	K_2CO_3	DMF	25
5	KOH	DMSO	43	15	NaOEt	DMF	31
6[c]	KOH	DMSO	Trace	16	NaOH	DMF	38
7	DBU	DMSO	-[e]	17	LiOH	DMF	56
8	NaH	DMSO	Trace	**18**	**KOH**	**DMF**	**69**
9	NaOH	DMSO	Trace	19	CH_3COONa	DMF	-[e]
10	LiOH	DMSO	Trace	20	DBU	DMF	-[e]

[a]All reactions were performed with **1** (0.25 mmol), **2** (0.375 mmol) and base (0.75 mmol) in solvent (5.0 mL) at 30-35 °C; [b]Reaction was performed at 60 °C; [c]2.5 mL DMSO was used; [d]Isolated yields are reported; [e]Complex mixture formation.

mixture along with major unreacted starting material was observed in all the cases. Further, ring transformation in the presence of potassium hydroxide in DMSO led to yield 43% of desired product (Table 1, Entry 5). However, use of lesser amount of DMSO provided, trace amount of product (Table 1, Entry 6). Use of DBU in DMSO provided complex mixture (Table 1, Entry 7). However, use of bases NaH, NaOH, LiOH and CH_3COONa separately in DMSO furnished trace amount (Table 1, Entries 8-11) of the desired product. Further, trial of K_2CO_3 in DMSO provided 19% of expected product (Table 1, Entry 12) while sodium ethoxide in EtOH gave a complex mixture (Table 1, Entry 13). Reactions using K_2CO_3, NaOEt, NaOH, and LiOH in DMF led to

Scheme 2. Scope of the Ring Contraction Strategy for the Synthesis of Spirobutenolides Using Nitromethane

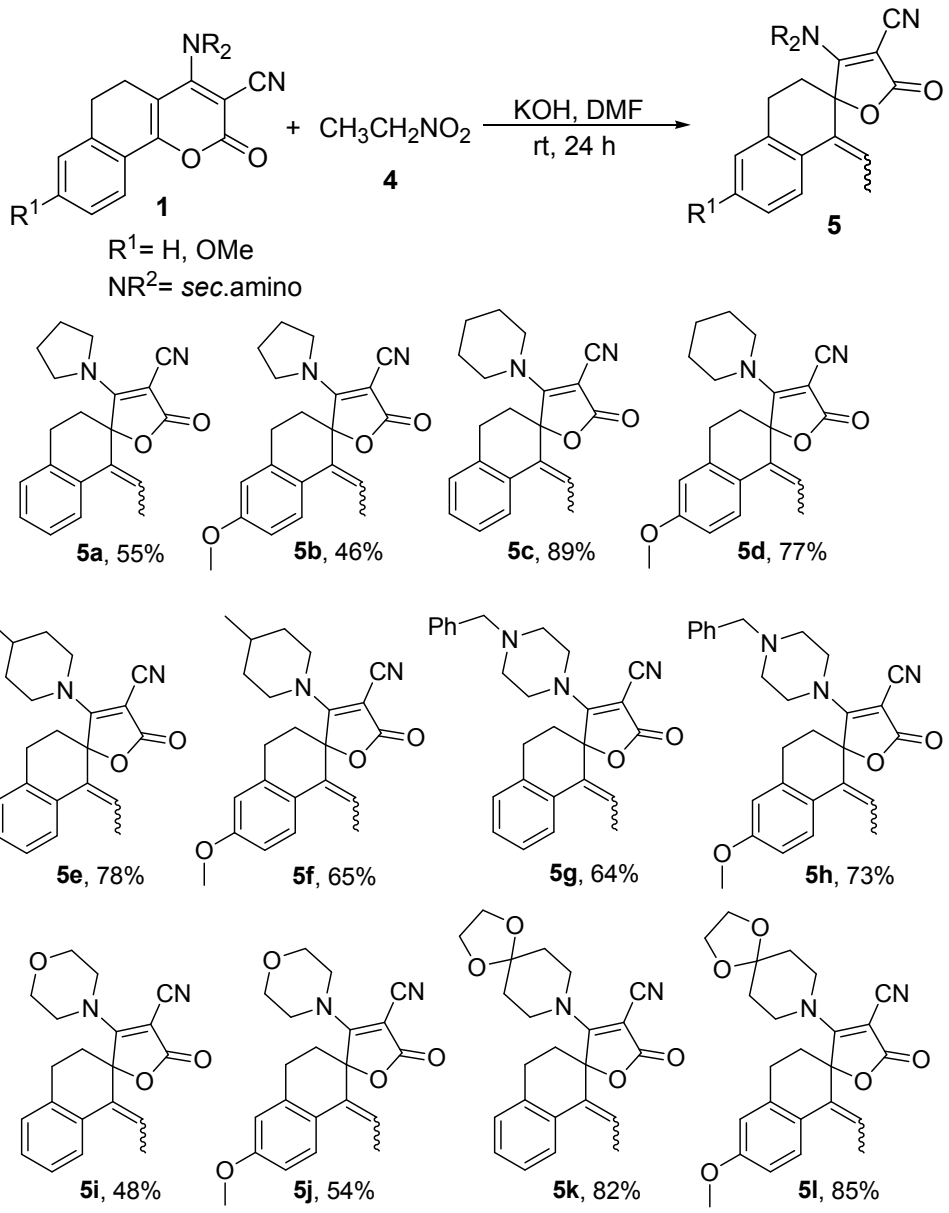




All reactions were performed by stirring 2-oxo-5,6-dihydro-2*H*-benzo[*h*]chromene-3-carbonitriles **1** (0.5 mmol) and nitromethane **2** (0.75 mmol) using KOH (1.5 mmol) in DMF (10.0 mL) at 30-35 °C.

yield 25, 31, 38 and 56% of expected product respectively (Table 1, Entries 14-17), and the best result was achieved by using KOH in DMF (69%) (Table 1, Entry 18). Use of CH_3COONa

Scheme 3. Scope of the Ring Contraction Strategy for the Synthesis of (*E*)- and (*Z*)-isomer of Spirobutenolides Using Nitroethane



All reactions were performed by stirring 2-oxo-5,6-dihydro-2*H*-benzo[*h*]chromene-3-carbonitriles **1** (0.5 mmol) and nitroethane **4** (0.75 mmol) using KOH (1.5 mmol) in DMF (10.0 mL) at 30-35 °C.

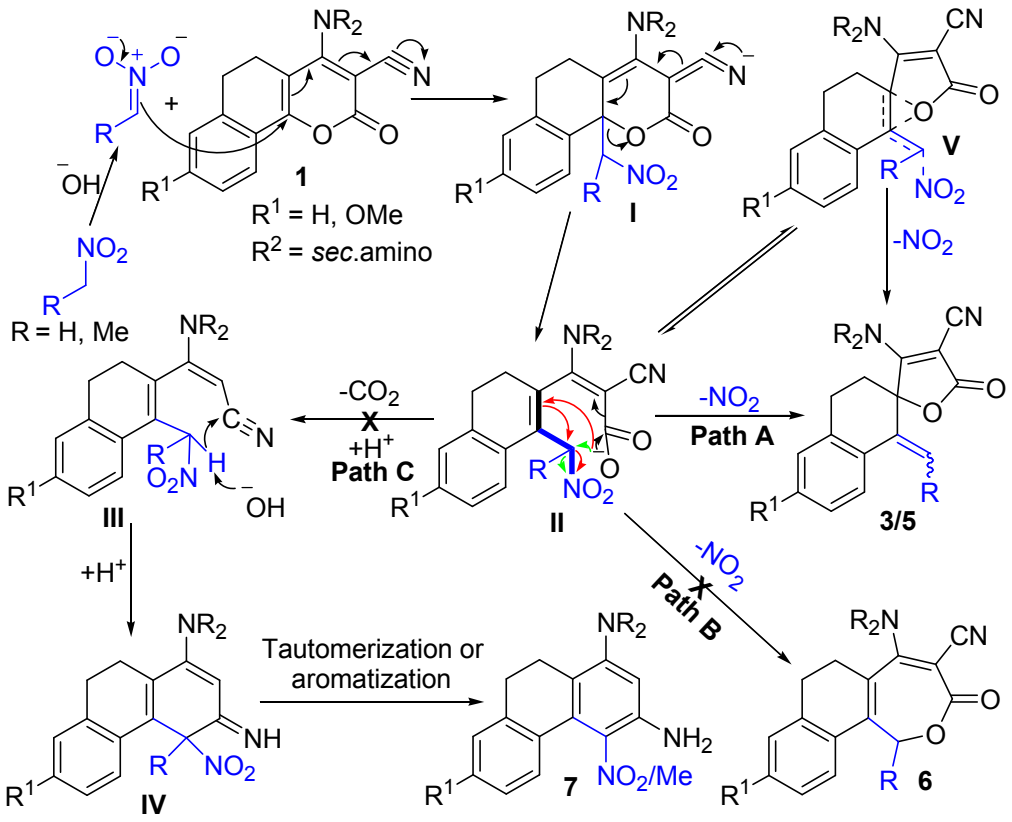
and DBU as base in DMF gave a complex mixture with major unreacted starting material (Table 1, Entries 19 and 20).

Under optimized conditions, reactions were carried out using differently functionalized 2-oxo-5,6-dihydro-2*H*-benzo[*h*]chromene-3-carbonitriles **1** with nitromethane **2** and desired spirobutenolides **3** afforded in 40-80% yield. The presence of electron donating substituent like methoxy group at position 8 of 2-oxobenzo[*h*]chromene enhanced the yield of spirobutenolides (Scheme 2).

The optimized condition was further generalized by using nitroethane as carbanion source in lieu of nitromethane and isolated the desired products in 46-89% yields (Scheme 3). This reaction provided a mixture of (*E*)- and (*Z*)-isomer in different ratio. In order to assign the geometry of the major and minor isomers, a compound **5d** was crystallized and structure was confirmed by single crystal X-ray (Figure S1, See SI). Then crystal was taken and ^{1}H NMR spectra were recorded to confirm the peak corresponding to the crystal. The structure of the crystal sample was confirmed unambiguously by single crystal X-ray diffraction as *E* isomer. Then, we also perform the ^{1}H NMR of the crude sample and compared with ^{1}H NMR of crystal. Using this result, we proposed that (*E*)-isomer is the major isomer in all mixtures of spirobutenolides obtained from nitroethane.

Interestingly, use of nitroethane gave the better yield of spirobutenolides as compared to nitromethane. Probably, the carbanion generated from nitromethane is highly reactive and stable compared to the carbanion produced from nitroethane and might be involved in the side reactions and reduced the yields. To further study the scope of reaction, we used 4-(methylthio)-2-oxo-5,6-dihydro-2*H*-benzo[*h*]chromene-3-carbonitrile as starting material with nitroethane under the similar reaction condition and we found that the starting material decomposed probably due to side reaction at C4.

Scheme 4. Proposed Mechanism for Ring Contraction of 2-Oxobenzo[*h*]chromenes 1 into Spirobutenolides

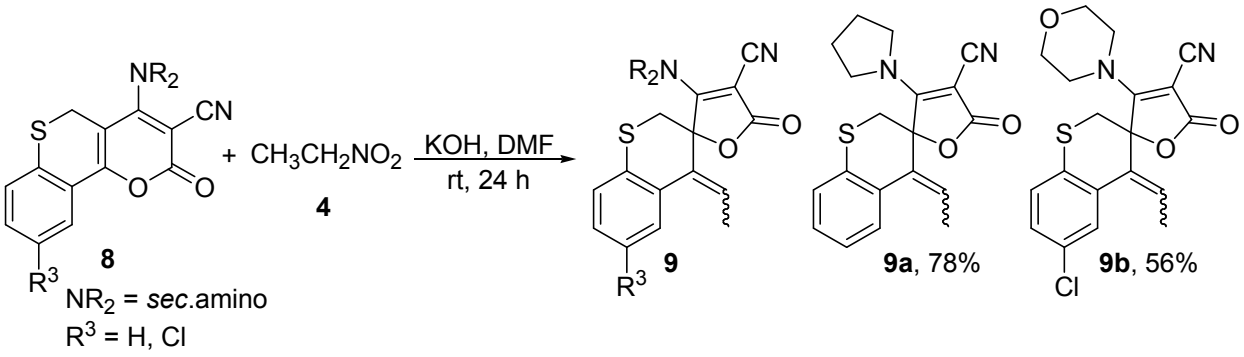


A plausible reaction mechanism is shown in Scheme 4. The reaction is possibly proceeding via attack of the nitronate anion generated from nitroalkane at C-10b position of the 2-oxo-5,6-dihydro-2*H*-benzo[*h*]chromene-3-carbonitriles through Michael addition, which probably provide the ring opening to generate the intermediate carboxylate ion **II** which can follow three paths A, B and C. It has been earlier reported that a stablilized carbanion could attack at the six-membered cyclic allylic nitro compound provides mixture of two denitrated regioisomers,[26] similarly we propose that the intramolecular allylic denitration occurs via nucleophilic conjugate substitution

reaction (S_N2') by attack of carboxylate ion at C-4a to provide spirobutenolides **3/5** as one regioisomer (Scheme 4, paths A). Alternatively, direct denitration was also possible by attack of carboxylate ion **II** at α position to nitro group affords functionalized oxepin-2(7H)-ones **6** as another regioisomer (Scheme 4, paths B). On the other hand, decarboxylation may occur via reversal of charge on carboxylate ion to provide intermediate **III**. In further step excess of base generates carbanion at α position to nitro group and cyclized by involvement of nitrile group to produce imine **IV**, which may tautomerize (in case of nitromethane) or aromatize through loss of nitro group (in case of nitroethane) to provide functionalized dihydrophenanthrenes **7** (Scheme 4, path C). Interestingly, only spirobutenolides was isolated and neither functionalized oxepinone nor dihydrophenanthrene formed during reaction. Therefore, we propose that the formation of five-membered butenolide ring is favorable than the seven-membered oxepinone ring under the given reaction conditions. We also carried out the reaction in presence of dimethyl sulfate in order to trap the carboxylate ion intermediate however, we isolated only the spirobutenolide product. This result indicates that as soon as the

ring is opened, recyclization takes place to yield spirobutenolide **3/5** through intermediate **V**.

Scheme 5. Scope of the Ring Contraction Strategy for the Synthesis of 4'-Ethylidene-5-oxo-3-sec.amino-5H-spiro[furan-2,3'-thiochroman]-4-carbonitriles 9

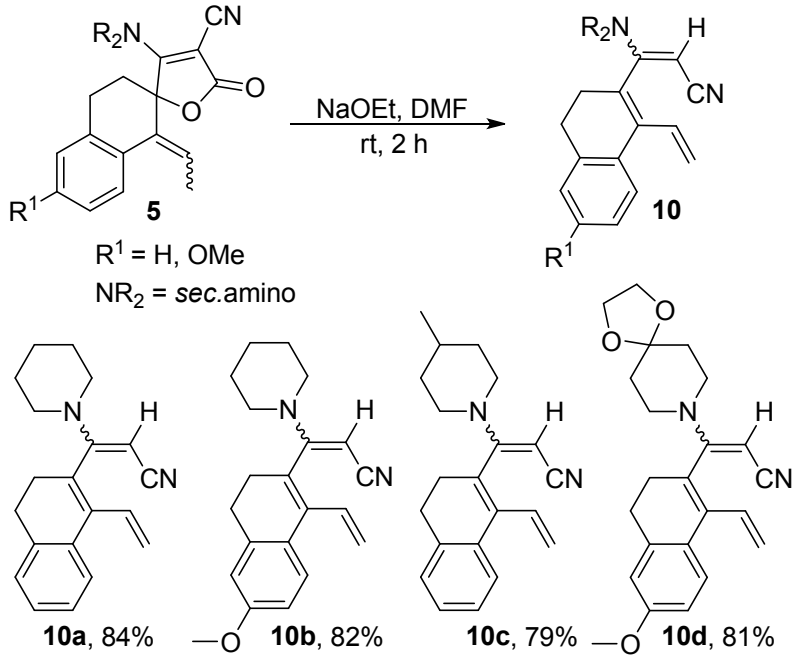


All reactions were performed by stirring 2-oxo-2,5-dihydrothiochromeno[4,3-b]pyran-3-carbonitriles **8** (0.5 mmol) and nitroethane **4** (0.75 mmol) using KOH (1.5 mmol) in DMF (10.0 mL) at 30-35 °C, precursors **8** were prepared using reported literature.[27]

To further expand the scope of this reaction we studied the ring transformation 4-*sec.*amino-2-oxo-2,5-dihydrothiochromeno[4,3-b]pyran-3-carbonitrile **8** by nitroethane **4** as shown in Scheme 5. This reaction successfully provided the desired spirobutenolide 4'-ethylidene-5-oxo-3-sec.amino-5*H*-spiro[furan-2,3'-thiochroman]-4-carbonitriles in high

yield. Interestingly, presence of an electron-withdrawing group (+*M* effect) such as chloro group at C-9 position enhances the yield (Scheme 5).

Scheme 6. Synthesis of Highly Substituted Trienes via Decarboxylative Rearrangement



All reactions were performed by stirring 1'-ethylidene-5-oxo-3',4'-dihydro-1'*H*,5*H*-spiro[furan-2,2'-naphthalene]-4-carbonitriles **5** (0.25 mmol) and sodium ethoxide (0.5 mmol) in DMF (2.0 mL) at 30-35 °C.

We also studied the synthetic application of 1'-ethylidene-5-oxo-3-*sec*.amino-3',4'-dihydro-1'*H*,5*H*-spiro[furan-2,2'-naphthalene]-4-carbonitriles under basic condition. Treatment of the compound with sodium ethoxide provides a functionalized trienes. The mixture of (*E*)- and (*Z*)-isomer of spirobutenolides **5** undergoes decarboxylative

rearrangement in presence of sodium ethoxide to produce the desired trienes (Scheme 6). On the other hand, no product was obtained under similar reaction condition from spirobutenolides generated from nitromethane. This reaction is under investigation.

CONCLUSION

In summary, a new method for synthesis of highly functionalized spirobutenolides has been developed through ring opening and relactonization (via ring contraction) at C-4a position of 2-oxobenzo[*h*]chromenes using nitroalkane as a carbanion source. Nitroethane provides (*E*)- and (*Z*)-isomer of spirobutenolides in different ratio depending on the substitution pattern. Most interesting finding in this reaction is base mediated chemoselective allylic denitration. Structure and geometry of compound was confirmed by single crystal X-ray. Moreover, spirobutenolides obtained from nitroethane undergoes decarboxylative rearrangement in presence of sodium ethoxide to afford trienes and can be used as a valuable precursor for the construction of different class of compounds of pharmacological importance.

EXPERIMENTAL SECTION

General remarks: Commercially available reagent and solvent purchased by Sigma Aldrich and Alfa Aesar were used directly without further purification. Reactions were monitored by analytical thin-layer chromatography (TLC). All reactions were conducted using dried glassware. All the starting materials were synthesized earlier except two and data is provided below. IR spectra were recorded on IR spectrophotometer and stretching frequencies were reported in wave number (cm^{-1}). The ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded in $CDCl_3$ solution using chloroform peak (7.24 ppm for ^{1}H and 77.0 ppm for ^{13}C) as reference. The coupling constant *J* are reported in Hz and signal patterns reported as s, singlet; br, broad signal; d, doublet; t, triplet; m, multiplet; dd, double doublet. High-resolution mass spectra were recorded on a quadrupole-time-of-flight mass spectrometer. In case of 1'-ethylidene-5-oxo-3-*sec*.amino-3',4'-dihydro-1'*H*,5*H*-spiro[furan-2,2'-naphthalene]-4-carbonitriles **5** and 4'-ethylidene-5-oxo-3-sec.amino-5*H*-spiro[furan-2,3'-thiochroman]-4-carbonitriles, we have isolated the mixture of (*E*)- and (*Z*)-isomer in different ratio and few sets of protons and carbons are appearing separately and is reported as mixture.

General Procedure for Synthesis of 1'-methylene/ethylidene-5-oxo-3',4'-dihydro-1'*H*,5*H*-spiro[furan-2,2'-naphthalene]-4-carbonitriles 3a-f, 5a-l and 4'-ethylidene-5-oxo-3-sec.amino-5H-spiro[furan-2,3'-thiochroman]-4-carbonitriles 9a-b. To a 25 mL round bottom flask equipped with small magnet, 2-oxo-5,6-dihydro-2*H*-benzo[*h*]chromene-3-carbonitriles/2-oxo-2,5-dihydrothiochromeno[4,3-b]pyran-3-carbonitriles **8** (0.5 mmol) (0.5 mmol) was dissolved in DMF (10.0 mL). Then powdered KOH (1.5 mmol, 87.0 mg) was added to the reaction mixture followed by drop-wise addition of nitromethane/nitroethane (0.75 mmol). The reaction mixture was stirred for 24 h at room temperature. After completion of reaction, excess of DMF was removed under reduced pressure, and the mixture was poured onto ice cold water (25.0 mL). The cold solution was neutralized with 10% HCl, and the obtained precipitate was filtered and dried under vacuum. The crude product was purified by alumina column chromatography using 20% ethyl acetate in hexane as an eluent. We observed that presence of DMF during work-up dissolved some of the product, so DMF must be completely removed under vacuum before addition of ice cold water.

General Procedure for Synthesis of 3-(1-Vinyl-3,4-dihydronaphthalen-2-yl)acrylonitrile 10a-d. A mixture of 1'-ethylidene-5-oxo-3',4'-dihydro-1'*H*,5*H*-spiro[furan-2,2'-naphthalene]-4-carbonitrile (0.25 mmol) and sodium ethoxide (0.5 mmol, 34.0 mg) in DMF (2.0 mL) was stirred for 2 h at room temperature. Completion of reaction was monitored by TLC. After completion, reaction mixture was poured onto crushed ice and neutralized with 10% HCl. The obtained precipitate was filtered, washed with water, dried and purified by silica gel column chromatography, using 10% ethyl acetate-hexane as an eluent.

2-Oxo-4-(1,4-dioxa-8-azaspiro[4.5]decan-8-yl)-5,6-dihydro-2*H*-benzo[*h*]chromene-3-carbonitrile (1a). Yield: 65% (2.37g); 0.13 R_f (40% ethyl acetate-hexane), yellow solid, mp: 205-207 °C; IR (KBr): 2965, 2212, 1707, 1616 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.88 (t, *J* = 5.6 Hz, 4H), 2.64 (t, *J* = 7.4 Hz, 2H), 2.86 (t, *J* = 7.4 Hz, 2H), 3.62 (t, *J* = 5.6 Hz, 4H), 3.98 (s, 4H), 7.20 (d, *J* = 7.6 Hz, 1H), 7.26-7.37 (m, 2H), 7.78 (d, *J* = 7.6 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 23.2, 27.8, 35.7, 49.8, 64.7, 81.7, 105.8, 108.9, 116.6, 124.6, 127.5, 127.6, 127.9, 131.6, 137.8, 157.4, 161.2, 167.4; HRMS (ESI) *m/z* calcd for $C_{21}H_{21}N_2O_4$ $[M + H]^+$ 365.1501, found 365.1504.

8-Methoxy-2-oxo-4-(1,4-dioxa-8-azaspiro[4.5]decan-8-yl)-5,6-dihydro-2*H*-benzo[*h*]chromene-3-carbonitrile (**1b**). Yield: 75% (2.96 g); 0.10 R_f (40% ethyl acetate-hexane), green solid, mp: 115-117 °C; IR (KBr): 2965, 2210, 1705, 1609 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.87 (s, 4H), 2.62 (t, J = 7.0 Hz, 2H), 2.82 (t, J = 7.0 Hz, 2H), 3.61 (s, 4H), 3.82 (s, 3H), 3.98 (s, 4H), 6.71 (s,1H), 6.78 (d, J = 7.6 Hz, 1H), 7.73 (d, J = 8.8 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$):δ 23.2, 28.2, 35.7, 49.8, 55.6, 64.7, 80.9, 105.8, 106.9, 112.5, 113.4, 116.8, 120.6, 126.7, 140.3, 157.9, 161.4, 162.4, 167.5; HRMS (ESI) *m/z* calcd for $C_{22}H_{23}N_2O_5$ $[M + H]^+$ 395.1607, found 395.1610.

1'-Methylene-5-oxo-3-(piperidin-1-yl)-3',4'-dihydro-1'*H*,5*H*-spiro[furan-2,2'-naphthalene]-4-carbonitrile (**3a**). Yield: 69% (111.0 mg); 0.22 R_f (40% ethyl acetate-hexane), light yellow solid, mp: 115-117 °C; IR (KBr): 2928, 2210, 1742, 1603 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.51-1.80 (m, 6H), 2.03-2.16 (m, 2H), 2.8 (d, J = 16.0 Hz, 1H), 3.13-3.27 (m, 3H), 3.72 (br, 1H), 4.22 (br, 1H), 5.35 (s, 1H), 5.97 (s, 1H), 7.19-7.31 (m, 3H), 7.62 (d, J = 6.9 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 23.2, 25.8, 25.9, 33.1, 50.9, 51.8, 69.3, 84.7, 114.9, 115.0, 124.3, 127.3, 128.8, 129.0, 131.1, 136.4,

139.5, 169.0, 171.8; HRMS (ESI) *m/z* calcd for $C_{20}H_{21}N_2O_2$ $[M + H]^+$ 321.1598, found 321.1583.

6'-Methoxy-1'-methylene-5-oxo-3-(piperidin-1-yl)-3',4'-dihydro-1'*H*,5*H*-spiro[furan-2,2'-naphthalene]-4-carbonitrile (**3b**).Yield: 80% (140.0 mg); 0.16 R_f (40% ethyl acetate-hexane), yellow solid, mp: 154-155 °C; IR (KBr): 2936, 2210, 1740, 1602 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.48-1.75 (m, 6H), 2.03-2.07 (m, 2H), 2.72 (d, *J* = 16.0 Hz, 1H), 3.06-3.25 (m, 3H), 3.68 (br, 1H), 3.78 (s, 3H), 4.17 (br, 1H), 5.15 (s, 1H), 5.77 (s, 1H), 6.66 (s, 1H), 6.77 (d, *J* = 6.4 Hz, 1H), 7.51 (d, *J* = 8.4 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 23.1, 25.7, 26.2, 33.0, 50.8, 51.8, 55.3, 69.1, 84.7, 112.2, 112.9, 113.8, 115.0, 123.7, 125.9, 138.0, 139.0, 160.0, 169.1, 171.8; HRMS (ESI) *m/z* calcd for $C_{21}H_{23}N_2O_3$ $[M + H]^+$ 351.1703, found 351.1700.

3-(4-Benzylpiperazin-1-yl)-1'-methylene-5-oxo-3',4'-dihydro-1'*H*,5*H*-spiro[furan-2,2'-naphthalene]-4-carbonitrile (**3c**). Yield: 40% (80.0 mg); 0.22 R_f (40% ethyl acetate-hexane), yellow solid, mp: 171-173 °C; IR (KBr): 2924, 2212, 1746, 1605 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.00-2.16 (m, 2H), 2.35-2.81 (m, 5H), 3.13-3.28 (m, 3H), 3.51 (s, 2H), 3.94 (br, 1H), 4.19 (br, 1H), 5.34 (s, 1H), 5.97 (s, 1H), 7.16-7.30 (m, 8H), 7.59 (d, *J*

= 6.8 Hz, 1H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 25.9, 33.2, 49.2, 50.5, 52.1, 52.3, 62.3, 70.1, 84.7, 114.8, 115.1, 124.3, 127.4, 127.5, 128.4, 128.8, 128.9, 129.1, 130.8, 136.3, 136.7, 139.5, 168.7, 172.1; HRMS (ESI) *m/z* calcd for $C_{26}H_{26}N_3O_2$ $[M + H]^+$ 412.2020, found 412.2015.

3-(4-Benzylpiperazin-1-yl)-6'-methoxy-1'-methylene-5-oxo-3',4'-dihydro-1'*H*,5*H*-spiro[furan-2,2'-naphthalene]-4-carbonitrile (**3d**). Yield: 55% (120.0 mg); 0.17 R_f (40% ethyl acetate-hexane), yellow solid, mp: 174-175 °C; IR (KBr): 2924, 2212, 1746, 1603 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.02-2.12 (m, 2H), 2.34 (br, 2H), 2.60-2.75 (m, 3H), 3.10-3.29 (m, 3H), 3.49 (s, 2H), 3.79 (s, 3H), 3.91 (br, 1H), 4.17 (br, 1H), 5.18 (s, 1H), 5.80 (s, 1H), 6.66 (s, 1H), 6.77 (d, *J* = 8.8 Hz, 1H); 7.24-7.29 (m, 5H), 7.52 (d, *J* = 8.8 Hz, 1H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 26.1, 33.1, 49.1, 50.4, 52.0, 52.2, 55.2, 62.1, 69.8, 84.7, 112.4, 112.9, 113.9, 114.8, 123.4, 125.9, 127.4, 128.3, 128.9, 136.7, 137.9, 138.9, 160.0, 168.7, 172.1; HRMS (ESI) *m/z* calcd for $C_{27}H_{28}N_3O_3$ $[M + H]^+$ 442.2125, found 442.2118.

1'-Methylene-5-oxo-3-(1,4-dioxa-8-azaspiro[4.5]decan-8-yl)-3',4'-dihydro-1'*H*,5*H*-spiro[furan-2,2'-naphthalene]-4-carbonitrile (**3e**). Yield: 58% (110.0 mg); 0.20 R_f (40%

ethyl acetate-hexane), white yellow solid, mp: 196-198 °C; IR (KBr): 2930, 2212, 1746, 1607 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.55-2.18 (m, 6H), 2.81 (d, *J* = 15.6 Hz, 1H), 3.11-3.40 (m, 3H), 3.84 (br, 1H), 3.96 (br, 4H), 4.34 (br, 1H), 5.34 (s, 1H), 5.98 (s, 1H), 7.19-7.31 (m, 3H), 7.60 (d, *J* = 7.2 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 25.8, 33.2, 34.9, 47.7, 48.7, 64.6, 69.9, 84.7, 105.0, 114.6, 114.9, 124.2, 127.3, 128.7, 129.0, 130.9, 136.3, 139.4, 168.7, 172.0; HRMS (ESI) *m/z* calcd for $C_{22}H_{23}N_2O_4$ $[M + H]^+$ 379.1652, found 379.1636.

6'-Methoxy-1'-methylene-5-oxo-3-(1,4-dioxa-8-azaspiro[4.5]decan-8-yl)-3',4'-dihydro-1'*H*,5*H*-spiro[furan-2,2'-naphthalene]-4-carbonitrile (**3f**). Yield: 69% (141.0 mg); 0.15 R_f (40% ethyl acetate-hexane), white solid, mp: 167-168 °C; IR (KBr): 2930, 2212, 1744, 1607 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.54-2.09 (m, 6H), 2.71 (d, *J* = 15.6 Hz, 1H), 3.04-3.33 (m, 3H), 3.77 (s, 4H), 3.91 (br, 4H), 4.28 (br, 1H), 5.13 (s, 1H), 5.75 (s, 1H), 6.65 (s, 1H), 6.75 (d, *J* = 8.8 Hz, 1H), 7.48 (d, *J* = 8.8 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 26.1, 33.1, 34.8, 47.6, 48.7, 55.2, 64.5, 69.7, 84.7, 105.0, 112.2, 112.9, 113.8, 114.6, 123.5, 125.8, 137.9, 138.9, 160.0, 168.7, 172.1; HRMS (ESI) *m/z* calcd for $C_{23}H_{25}N_2O_5$ $[M + H]^+$ 409.1758, found 409.1771.

1'-Ethylidene-5-oxo-3-(pyrrolidin-1-yl)-3',4'-dihydro-1'*H*,5*H*-spiro[furan-2,2'-naphthalene]-4-carbonitrile (**5a**). Yield: 55% (88.0 mg); 0.23 R_f (40% ethyl acetate-hexane), white solid, mp: 185-186 °C; IR (KBr): 2949, 2210, 1740, 1605 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.76-2.15 (m, 9H), 2.73 (d, *J* = 15.2 Hz, 1H), 2.96-3.11 (m, 2H), 3.29-3.47 (m, 1H), 3.91-4.07 (m, 2H), 6.04 (q, *J* = 7.6 Hz, 0.75H [for *E*-isomer]), 6.43 (q, *J* = 7.6 Hz, 0.25H [for *Z*-iosmer]), 7.14-7.30 (m, 3H), 7.39-7.43 (m, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 14.6, 16.3, 24.5, 24.6, 25.5, 25.6, 26.3, 26.7, 34.5, 37.2, 50.7, 51.2, 70.3, 84.4, 86.3, 115.3, 124.7, 126.4, 127.4, 127.6, 127.8, 128.0, 128.7, 130.1, 130.7, 131.5, 131.9, 133.0, 137.0, 139.2, 169.5, 172.0, 172.5; HRMS (ESI) *m/z* calcd for $C_{20}H_{21}N_2O_2$ $[M + H]^+$ 321.1598, found 321.1589.

1'-Ethylidene-6'-methoxy-5-oxo-3-(pyrrolidin-1-yl)-3',4'-dihydro-1'*H*,5*H*-spiro[furan-2,2'-naphthalene]-4-carbonitrile (**5b**). Yield: 46% (80.0 mg); 0.20 R_f (40% ethyl acetate-hexane), white yellow solid, mp: 185-186 °C; IR (KBr): 2949, 2210, 1740, 1603 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ1.74-2.10 (m, 9H), 2.63-2.68 (m, 1H), 2.95-3.08 (m, 2H), 3.28-3.46 (m, 1H), 3.80 (s, 3H), 3.88-4.02 (m, 2H), 5.89 (q, *J* = 7.6 Hz, 0.75H [for *E*-isomer]), 6.27 (q, *J* = 7.6 Hz, 0.25H [for *Z*-isomer]), 6.65-6.81 (m, 2H), 7.30-7.33 (m,

1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ14.5, 16.2, 24.5, 25.5, 25.6, 26.6, 27.1, 34.4, 37.2, 50.5, 50.7, 51.2, 55.3, 70.3, 86.4, 87.1, 112.1, 112.5, 113.1, 113.5, 115.3, 124.4, 126.1, 127.8, 130.0, 130.5, 131.1, 140.9, 158.9, 159.1, 169.5, 172.1; HRMS (ESI) *m/z* calcd for $C_{21}H_{23}N_2O_3$ $[M + H]^+$ 351.1703, found 351.1711.

1'-Ethylidene-5-oxo-3-(piperidin-1-yl)-3',4'-dihydro-1'*H*,5*H*-spiro[furan-2,2'-naphthalene]-4-carbonitrile (**5c**). Yield: 89% (149.0 mg); 0.28 R_f (40% ethyl acetate-hexane), white solid, mp: 153-155 °C; IR (KBr): 2943, 2208, 1742, 1605 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.46-1.93 (m, 7H), 2.06 (d, *J* = 16.8 Hz, 3H), 2.13-2.19 (m, 1H), 2.70-2.75 (m, 1H), 2.95-3.13 (m, 2H), 3.38-3.52 (m, 2H), 4.34-4.49 (m, 1H), 6.04 (q, *J* = 7.6 Hz, 0.70H [for *E*-iosmer]), 6.42 (q, *J* = 7.6 Hz, 0.30H [for *Z*-iosmer]), 7.15-7.30 (m, 3H), 7.38-7.41 (m, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 14.6, 16.3, 23.3, 26.0, 26.3, 26.8, 35.3, 37.7, 51.0, 51.6, 69.2, 84.5, 86.3, 87.2, 115.1, 124.5, 126.4, 127.5, 127.8, 127.9, 128.0, 128.2, 128.5, 129.7, 131.5, 132.3, 132.6, 134.9, 136.8, 138.9, 169.4, 172.3, 172.8; HRMS (ESI) *m/z* calcd for $C_{21}H_{23}N_2O_2$ $[M + H]^+$ 335.1754, found 335.1778.

1'-Ethylidene-6'-methoxy-5-oxo-3-(piperidin-1-yl)-3',4'-dihydro-1'*H*,5*H*-spiro[furan-2,2'-naphthalene]-4-carbonitrile (**5d**). Yield: 77% (141.0 mg); 0.20 R_f (40% ethyl acetate-hexane), white solid, mp: 187-189 °C; IR (KBr): 2943, 2208, 1742, 1605 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.43-1.85 (m, 7H), 1.99 (d, *J* = 7.2 Hz, 3H), 2.08-2.13 (m, 1H), 2.62-2.68 (m, 1H), 2.81-3.05 (m, 2H), 3.24 (br, 1H), 3.49 (br, 1H), 3.81 (s, 3H), 4.30 (br, 1H), 5.89 (q, *J* = 7.2 Hz, 0.85H [for *E*-iosmer]), 6.25 (q, *J* = 7.2 Hz, 0.15H [for *Z*-iosmer]), 6.73-6.80 (m, 2H), 7.30 (d, *J* = 8.4 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 16.2, 23.3, 25.9, 27.1, 35.1, 50.9, 51.6, 55.2, 69.0, 86.4, 112.1, 113.3, 115.1, 124.0, 127.4, 129.8, 131.8, 140.5, 159.0, 169.6, 172.4 for *E*-iosmer, 14.4, 37.6, 52.7, 68.6, 84.5, 112.6, 125.9, 126.5, 138.2, 173.0 for *Z*-iosmer; HRMS (ESI) *m/z* calcd for $C_{22}H_{25}N_2O_3$ $[M + H]^+$ 365.1860, found 365.1869.

1'-Ethylidene-3-(4-methylpiperidin-1-yl)-5-oxo-3',4'-dihydro-1'*H*,5*H*-spiro[furan-2,2'-naphthalene]-4-carbonitrile (**5e**). Yield: 78% (136.0 mg); 0.4 R_f (40% ethyl acetate-hexane), light pink solid, mp: 160-162 °C; IR (KBr): 2928, 2210, 1742, 1605 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 0.98 (d, *J* = 6.8 Hz, 3H), 1.30-2.17 (m, 10H), 2.70-2.86 (m, 2H), 3.02-3.17 (m, 2H), 3.31-3.54 (m, 1H), 4.57-4.84 (m, 1H), 6.05 (q, *J* = 7.6 Hz, 0.70H

[for *E*-iosmer]), 6.42 (q, *J* = 7.6 Hz, 0.30H [for *Z*-iosmer]), 7.15-7.29 (m, 3H), 7.34-7.41 (m, 1H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 14.5, 16.2, 21.4, 26.2, 26.7, 30.2, 33.9, 34.5, 35.1, 37.6, 50.3, 51.0, 68.5, 68.9, 84.4, 86.2, 115.0, 124.4, 126.4, 127.4, 127.8, 128.0, 128.1, 128.3, 129.6, 131.4, 131.8, 132.2, 132.5, 134.9, 136.7, 138.8, 169.5, 172.2, 172.7; HRMS (ESI) *m/z* calcd for $C_{22}H_{25}N_2O_2$ $[M + H]^+$ 349.1911, found 349.1916.

1'-Ethylidene-6'-methoxy-3-(4-methylpiperidin-1-yl)-5-oxo-3',4'-dihydro-1'*H*,5*H*-spiro[furan-2,2'-naphthalene]-4-carbonitrile (**5f**). Yield: 65% (123.0 mg); 0.30 R_f (40% ethyl acetate-hexane), yellow solid, mp: 72-73 °C; IR (KBr): 2953, 2210, 1744, 1607 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.94 (d, *J* = 6.4 Hz, 3H), 1.26-2.10 (m, 10H), 2.61-2.81 (m, 2H), 2.95-3.12 (m, 2H), 3.37-3.53 (m, 1H), 3.77 (s, 1H [for *Z*-iosmer]), 3.80 (s, 2H [for *E*-iosmer]), 4.53-4.77 (m, 1H), 5.88 (q, *J* = 7.2 Hz, 0.64H [for *E*-iosmer]), 6.25 (q, *J* = 8.0 Hz, 0.36H [for*Z*-iosmer]), 6.64-6.79 (m, 2H), 7.29 (d, *J* = 8.0 Hz, 1H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 14.4, 16.2, 21.5, 26.5, 27.0, 29.6, 30.2, 34.0, 34.5, 35.1, 37.6, 50.3, 51.1, 55.2, 68.6, 84.5, 86.3, 112.1, 112.6, 113.3, 113.5, 115.2, 124.0, 125.8, 127.4, 129.7, 130.2, 131.3, 131.7, 138.3, 140.5, 159.0, 159.2, 169.6, 172.3, 172.9; HRMS (ESI) *m/z* calcd for $C_{23}H_{27}N_2O_3$ $[M + H]^+$ 379.2016, found 379.2022.

3-(4-Benzylpiperazin-1-yl)-1'-ethylidene-5-oxo-3',4'-dihydro-1'*H*,5*H*-spiro[furan-2,2'-naphthalene]-4-carbonitrile(**5g**). Yield: 64% (0.135 g); 0.25 R_f (40% ethyl acetate-hexane), yellow solid, mp: 71-73 °C; IR (KBr): 2924, 2212, 1746, 1607 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.79-1.90 (m, 2H), 2.04 (d, *J* = 7.2 Hz, 3H), 2.14-2.80 (m, 6H), 2.99-3.26 (m, 2H), 3.46-3.54 (m, 2H), 3.74-3.87 (m, 1H), 4.16-4.35 (m, 1H), 6.02 (q, *J* = 7.2 Hz, 0.70H [for *E*-iosmer]), 6.40 (q, *J* = 7.2 Hz, 0.30H [for *Z*-iosmer]), 7.19-7.37 (m, 9H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 14.6, 16.3, 26.2, 26.7, 35.2, 37.7, 49.2, 50.1, 52.2, 52.6, 62,2, 69.4, 69.8, 84.4, 86.3, 114.8, 114.9, 124.4, 126.5, 127.5, 127.8, 127.9, 128.0, 128.2, 128.3, 128.5, 128.9, 129.9, 131.3, 131.8, 132.3, 132.6, 134.5, 136.6, 136.7, 138.8, 169.1, 169.2, 172.7, 173.4; HRMS (ESI) *m/z* calcd for $C_{27}H_{28}N_3O_2$ $[M + H]^+$ 426.2176, found 426.2179.

3-(4-Benzylpiperazin-1-yl)-1'-ethylidene-6'-methoxy-5-oxo-3',4'-dihydro-1'*H*,5*H*-spiro[furan-2,2'-naphthalene]-4-carbonitrile (**5h**). Yield: 73% (165.0 mg); 0.20 R_f (40% ethyl acetate-hexane), yellow solid, mp: 72-73 °C; IR (KBr): 2922, 2212, 1746, 1607 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.79-1.87 (m, 2H), 2.00 (d, *J* = 7.2 Hz, 3H), 2.12-2.78 (m, 6H), 2.98-3.26 (m, 2H), 3.38-3.54 (m, 2H), 3.75-3.87 (m, 4H), 4.15-4.35 (m,

1H), 5.89 (q, *J* = 7.2 Hz, 0.68H [for *E*-iosmer]), 6.27 (q, *J* = 7.2 Hz, 0.32H [for *Z*-iosmer]), 6.66-6.80 (m, 2H) 7.27-7.34 (m, 6H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ14.4, 16.2, 26.4, 27.0, 35.2, 37.7, 49.1, 50.1, 52.2, 52.6, 55.2, 62.2, 69.3, 69.7, 84.4, 86.4, 112.2, 112.7, 113.3, 113.5, 114.9, 115.0, 123.8, 125.8, 127.1, 127.4, 127.6, 128.3, 128.8, 129.8, 130.1, 131.3,131.8, 136.6, 136.7, 138.2, 140.5, 159.0, 159.3, 169.2, 172.8, 173.5; HRMS (ESI) *m/z* calcd for $C_{28}H_{30}N_3O_3$ $[M + H]^+$ 456.2282, found 456.2283.

1'-Ethylidene-3-morpholino-5-oxo-3',4'-dihydro-1'*H*,5*H*-spiro[furan-2,2'-naphthalene]-4-carbonitrile (**5i**). Yield: 48% (80.0 mg); 0.20 R_f (40% ethyl acetate-hexane), yellow solid, mp: 155-157 °C; IR (KBr): 2924, 2212, 1744, 1605 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.80-1.87 (m, 1H), 1.90 (d, *J* = 7.2 Hz, 1H [for *Z*-iosmer]), 2.07 (d, *J* = 6.8 Hz, 2H [for *E*-iosmer]), 2.19 (d, *J* = 14.4 Hz, 1H), 2.74 (d, *J* = 13.6 Hz, 1H), 3.02-4.32 (m, 9H), 6.07 (q, *J* = 6.8 Hz, 0.60H [for *E*-iosmer]), 6.45 (q, *J* = 7.2 Hz, 0.40H [for *Z*-iosmer]), 7.17-7.37 (m, 4H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 14.6, 16.3, 26.1, 26.6, 35.2, 37.7, 49.4, 50.3, 66.1, 66.3, 69.9, 70.3, 84.4, 86.4, 114.7, 124.4, 126.6, 127.6, 128.0, 128.1, 128.2, 128.3, 128.5, 130.1, 131.2, 131.7, 132.2, 132.9, 134.4, 136.8,

138.8, 168.8, 168.9, 172.9, 173.6; HRMS (ESI) *m/z* calcd for $C_{20}H_{21}N_2O_3$ $[M + H]^+$ 337.1547, found 337.1558.

1'-Ethylidene-6'-methoxy-3-morpholino-5-oxo-3',4'-dihydro-1'*H*,5*H*-spiro[furan-2,2'-naphthalene]-4-carbonitrile (**5j**). Yield: 54% (98.0 mg); 0.16 R_f (40% ethyl acetate-hexane), white solid, mp: 170-171 °C; IR (KBr): 2922, 2212, 1740, 1601 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.79-1.82 (m, 1H), 1.87 (d, *J* = 7.6 Hz, 1H [for *Z*-iosmer]), 2.03 (d, *J* = 6.8 Hz, 2H [for *E*-iosmer]), 2.16 (d, *J* = 13.6 Hz, 1H), 2.69 (d, *J* = 14.4 Hz, 1H), 3.01-4.32 (m, 12H), 5.94 (q, *J* = 6.8 Hz, 0.75H [for *E*-iosmer]), 6.31 (q, *J* = 7.6 Hz, 0.25H [for *Z*-iosmer]), 6.69-6.82 (m, 2H), 7.27-7.31 (m, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 14.5, 16.3, 26.5, 27.1, 35.2, 37.8, 49.3, 50.4, 55.3, 66.2, 68.8, 70.4, 84.4, 86.3, 112.4, 112.8, 113.5, 113.7, 114.7, 123.7, 125.9, 127.0, 127.9, 129.9, 130.4, 131.8, 138.4, 140.6, 159.2, 168.9, 173.1; HRMS (ESI) *m/z* calcd for $C_{21}H_{23}N_2O_4$ $[M + H]^+$ 367.1652, found 367.1658.

1'-Ethylidene-5-oxo-3-(1,4-dioxa-8-azaspiro[4.5]decan-8-yl)-3',4'-dihydro-1'*H*,5*H*-spiro[furan-2,2'-naphthalene]-4-carbonitrile (**5k**). Yield: 82% (160.0 mg); 0.24 R_f (40% ethyl acetate-hexane), yellow solid, mp: 203-204 °C; IR (KBr): 2926, 2212, 1746, 1607

cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.55-1.62 (m, 2H), 1.83-1.95 (m, 4H), 2.05 (d, *J* = 7.2 Hz, 2H), 2.15-2.20 (m, 1H), 2.70-2.76 (m, 1H), 3.00-3.45 (m, 3H), 3.64-3.71 (m, 1H), 3.90-4.01 (m, 4H), 4.43-4.57 (m, 1H), 6.04 (q, *J* = 7.2 Hz, 0.60H [for *E*-iosmer]), 6.42 (q, *J* = 7.2 Hz, 0.40H [for *Z*-iosmer]), 7.15-7.28 (m, 3H), 7.36-7.39 (m, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 14.6, 16.3, 26.3, 26.8, 35.2, 35.4, 37.9, 47.8, 48.6, 64.6, 64.8, 69.6, 70.0, 84.6, 86.4, 105.1, 105.2, 114.7, 114.9, 124.4, 126.5, 127.6, 127.9, 128.0, 128.1, 128.3, 128.4, 129.8, 131.4, 131.7, 132.1, 132.9, 134.8, 136.8, 138.9, 169.1, 169.2, 172.6, 173.3; HRMS (ESI) *m/z* calcd for $C_{23}H_{25}N_2O_4$ $[M + H]^+$ 393.1809, found 393.1814.

1'-Ethylidene-6'-methoxy-5-oxo-3-(1,4-dioxa-8-azaspiro[4.5]decan-8-yl)-3',4'-dihydro-1'*H*,5*H*-spiro[furan-2,2'-naphthalene]-4-carbonitrile (**5l**). Yield: 85% (179.0 mg); 0.15 R_f (40% ethyl acetate-hexane), white solid, mp: 199-200 °C; IR (KBr): 2926, 2212, 1744, 1605 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.51-1.59 (m, 2H), 1.80 (d, *J* = 7.2 Hz, 1H [for *Z*-iosmer]), 1.82-1.91 (m, 3H), 1.98 (d, *J* = 7.2 Hz, 2H [for *E*-iosmer]), 2.09-2.14 (m, 1H), 2.61-2.68 (m, 1H), 2.95-3.67 (m, 4H), 3.77 (s, 1H [for *Z*-iosmer]), 3.80 (s, 2H [for *E*-iosmer]), 3.87-3.98 (m, 4H), 4.39-4.53 (m, 1H), 5.88 (q, *J* = 7.2 Hz, 0.64H [for *E*-

iosmer]), 6.25 (q, *J* = 7.2 Hz, 0.36H [for *Z*-iosmer]), 6.65-6.78 (m, 2H), 7.27 (dd, *J* = 8.8, 2.8 Hz, 1H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 14.4, 16.2, 26.6, 27.1, 35.0, 35.3, 37.9, 47.8, 48.6, 55.3, 64.6, 64.7, 69.5, 69.9, 84.6, 86.4, 105.1, 105.2, 112.2, 112.7, 113.4,113.6, 114.8, 114.9, 123.9, 125.8, 127.4, 127.6, 129.7, 130.4, 131.1, 131.6, 138.3, 140.6, 159.1, 159.3, 169.2, 169.3, 172.7, 173.4; HRMS (ESI) *m/z* calcd for $C_{24}H_{27}N_2O_5$ $[M + H]^+$ 423.1914, found 423.1916.

4'-Ethylidene-5-oxo-3-(pyrrolidin-1-yl)-5H-spiro[furan-2,3'-thiochroman]-4-carbonitrile (**9a**). Yield: 78% (131.0 mg); 0.14 R_f (40% ethyl acetate-hexane), white solid, mp: 189-191 °C; IR (KBr): 2925, 2212, 1745, 1610 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.75-2.09 (m, 7H), 2.80-3.20 (m, 3H), 3.42-3.53 (m, 1H), 3.92-4.03 (m, 2H), 6.05 (q, *J* = 7.2 Hz, 0.80H [for *E*-isomer]), 6.32 (q, *J* = 7.6 Hz, 0.20H [for *Z*-iosmer]), 7.18-7.41 (m, 4H), 7.39-7.43 (m, 1H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 15.2, 16.2, 24.7, 25.7, 38.8, 41.2, 51.7, 52.4, 70.6, 86.4, 89.1, 115.1, 126.7, 127.3, 127.6, 128.0, 128.2, 129.2, 130.0, 130.6, 131.2, 132.2, 133.2, 134.3, 135.9, 136.8, 168.7, 169.9; HRMS (ESI) *m/z* calcd for $C_{19}H_{19}N_2O_2S$ $[M + H]^+$ 339.1162, found 339.1155.

6'-Chloro-4'-ethylidene-3-morpholino-5-oxo-5H-spiro[furan-2,3'-thiochroman]-4-carbonitrile (**9b**). Yield: 56% (108.6 mg); 0.20 R_f (40% ethyl acetate-hexane), white solid, mp: 116-118 °C; IR (KBr): 2925, 2213, 1747, 1607 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.90 (d, *J* = 7.6 Hz, 1H [for *Z*-iosmer]), 1.96 (d, *J* = 7.2 Hz, 2H [for *E*-iosmer]), 2.87-4.23 (m, 10H), 6.09 (q, *J* = 7.2 Hz, 0.65H [for *E*-iosmer]), 6.38 (q, *J* = 7.6 Hz, 0.35H [for *Z*-iosmer]), 7.17-7.39 (m, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 15.2, 16.2, 39.2, 41.4, 49.9, 51.1, 66.2, 66.4, 70.8, 71.1, 85.8, 89.1, 114.4, 126.6, 128.4, 128.7, 130.2, 130.6, 131.3, 131.4, 131.7, 132.4, 132.7, 132.8, 133.3, 133.8, 134.4, 137.6, 138.1, 167.7, 168.0, 170.6, 171.0; HRMS (ESI) *m/z* calcd for $C_{19}H_{18}ClN_2O_3S$ $[M + H]^+$ 389.0727, found 389.0742.

3-(Piperidin-1-yl)-3-(1-vinyl-3,4-dihydronaphthalen-2-yl)acrylonitrile (**10a**). Yield: 84% (61.0 mg); 0.15 R_f (10% ethylacetate-hexane), yellow solid, mp: 68-69 °C; IR (KBr): 2934, 2191, 1553 cm^{-1}; ^1H NMR (400 MH_Z , $CDCl_3$): δ 1.55 (br, 6H), 2.26-2.34 (m, 1H), 2.49-2.57 (m, 1H), 2.72-2.80 (m, 1H), 2.93-3.01 (m, 1H), 3.20 (br, 4H), 3.95 (s, 1H), 5.38 (dd, *J* = 11.2 Hz, *J* = 1.6 Hz, 1H), 5.44 (dd, *J* = 17.6 Hz, *J* = 1.6 Hz, 1H), 6.55 (dd, *J* = 17.6 Hz, *J* = 11.2 Hz, 1H), 7.17-7.19 (m, 3H), 7.44-7.47 (m, 1H); $^{13}C\{^1H\}$ NMR (100

MH_Z, $CDCl_3$): δ 24.0, 25.6, 28.2, 29.4, 48.0, 62.0, 119.4, 122.1, 126.1, 126.2, 127.5, 127.7, 130.8, 132.2, 133.1, 136.4, 137.0, 165.6; HRMS (ESI) *m/z* calcd for $C_{20}H_{23}N_2$ [M + H]$^+$ 291.1861, found 291.1862.

3-(6-Methoxy-1-vinyl-3,4-dihydronaphthalen-2-yl)-3-(piperidin-1-yl)acrylonitrile (**10b**). Yield: 82% (66.0 mg); 0.09 R_f (10% ethylacetate-hexane), viscous liquid; IR (KBr): 2927, 2192, 1557 cm^{-1}; ^{1}H NMR (400 MH_Z , $CDCl_3$): δ 1.56 (br, 6H), 2.24-2.32 (m, 1H), 2.46-2.54 (m, 1H), 2.69-2.76 (m, 1H), 2.90-3.98 (m, 1H), 3.18 (br, 4H), 3.79 (s, 3H), 3.94 (s, 1H), 5.35 (dd, *J* = 11.6 Hz, *J* = 1.6 Hz, 1H), 5.42 (dd, *J* = 17.6 Hz, *J* = 1.6 Hz, 1H), 6.53 (dd, *J* = 17.6 Hz, *J* = 11.6 Hz, 1H), 6.68-6.72 (m, 2H), 7.38 (d, *J* = 8.4 Hz, 1H); ^{13}C{^{1}H} NMR (100 MH_Z, $CDCl_3$): δ 24.2, 25.7, 28.3, 28.8, 48.0, 55.4, 62.2, 111.0, 113.7, 119.3, 122.4, 126.3, 127.7, 128.6, 132.6, 136.2, 139.0, 159.2, 165.9; HRMS (ESI) *m/z* calcd for $C_{21}H_{25}N_2O$ [M + H]$^+$ 321.1961, found 321.1963.

3-(4-Methylpiperidin-1-yl)-3-(1-vinyl-3,4-dihydronaphthalen-2-yl) (**10c**). Yield: 79% (60.0 mg); 0.17 R_f (10% ethylacetate-hexane), yellow solid, mp: 65-67 °C; IR (KBr): 2925, 2192, 1556 cm^{-1}; ^{1}H NMR (400 MH_Z , $CDCl_3$): δ 0.94 (d, *J* = 6.4 Hz, 3H), 1.12-1.19 (m, 2H), 1.55-1.66 (m, 3H), 2.27-2.35 (m, 1H), 2.49-2.56 (m, 1H), 2.73-2.84 (m,

3H), 2.93-3.01 (m, 1H), 3.59 (d, J = 12 Hz, 2H), 3.96 (s, 1H), 5.38 (d, J = 11.2 Hz, 1H), 5.44 (d, J = 18.0 Hz, 1H), 6.55 (dd, J = 18.0 Hz, J = 11.2 Hz, 1H), 7.17-7.19 (m, 3H), 7.45-7.46 (m, 1H); $^{13}C\{^1H\}$ NMR (100 MH_Z, $CDCl_3$): δ 21.8, 28.3, 29.8, 30.8, 33.9, 47.4, 62.3, 119.6, 122.2, 126.3, 126.4, 127.6, 127.9, 131.0, 132.3, 133.3, 136.5, 137.1, 165.7; HRMS (ESI) *m/z* calcd for $C_{21}H_{25}N_2$ $[M + H]^+$ 305.2012, found 305.2022.

3-(6-Methoxy-1-vinyl-3,4-dihydronaphthalen-2-yl)-3-(1,4-dioxa-8-azaspiro[4.5]decan-8-yl)acrylonitrile (**10d**). Yield: 81% (77.0 mg); 0.22 R_f (30% ethylacetate-hexane), white solid, mp: 115-117 °C; IR (KBr): 2959, 2193, 1558 cm^{-1}; ^1H NMR (400 MHZ , $CDCl_3$): δ 1.69 (br, 4H), 2.24-2.32 (m, 1H), 2.48-2.55 (m, 1H), 2.69-2.76 (m, 1H), 2.90-2.98 (m, 1H), 3.32 (t, J = 5.6 Hz, 4H), 3.79 (s, 3H), 3.95 (s, 4H), 4.01 (s, 1H), 5.36 (dd, J = 11.2 Hz, J = 1.6 Hz, 1H), 5.42 (dd, J = 17.6 Hz, J = 1.6 Hz, 1H), 6.52 (dd, J = 17.6 Hz, J = 11.2 Hz, 1H), 6.69-6.72 (m, 2H), 7.38 (d, J = 8.4 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHZ, $CDCl_3$): δ 28.1, 28.7, 34.6, 45.2, 55.3, 63.6, 64.5, 106.4, 110.9, 113.6, 119.5, 121.6, 126.1, 127.6, 128.0, 132.3, 136.5, 138.9, 159.2, 165.5; HRMS (ESI) *m/z* calcd for $C_{23}H_{27}N_2O_3$ $[M + H]^+$ 379.2016, found 379.2023.

ASSOCIATED CONTENT

Supporting Information Available: ^{1}H and ^{13}C NMR spectra of all the synthesized compounds are available in supporting information. Crystallographic detail for **5d** is also given in SI. This material is available free of charge via the Internet at http://pubs.acs.org

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All the authors contributed the work in order to complete the work. RP and VJR were involved in designing of project and all author played role in writing the manuscript.

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