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Efficient atom economical one-pot multicomponent synthesis of densely functionalized 4*H*-chromene derivatives

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ABSTRACT

A sequential one-pot, atom economical three component reaction yielding medicinally promising ethyl 2-amino-3-cyano-4-(2-ethoxy-2-oxoethyl)-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-4-carboxylate derivatives (**4a**–**f**) through a tandem Michael addition–cyclization reaction starting with structurally diverse cyclohexane-1,3-dione, diethyl acetylene dicarboxylate, and malononitrile has been carried out in different organic bases under solvent free condition for the optimization of maximum yield. All the formed 4*H*-chromenes were characterized by spectral and X-ray methods.

1. Introduction

Highly functionalized 4*H*-chromenes occur commonly in numerous natural compounds,[1,2] showing significant biological activities and extensive applications in pharmaceutical uses,[3] such as anticoagulant, spasmolytic, diuretic, antiancaphylactia, and anticancer.[4–8] Besides, 4*H*-chromenes can be employed as cosmetics or pigments,[9,10] and utilized as potential biodegradable agrochemicals.[11] These compounds have potential application as cognitive enhancers for the treatment of neurodegenerative diseases, including Alzheimer's disease, as well as for the treatment of schizophrenia and myoclonus.[1] Chromene pharmacophore can also serve as useful building blocks in the generation of a variety of natural products showing molluscicidal, antibacterial, antitumor, antiallergic, antibiotic, hypolipidemic, and immunomodulating activities.[12–14] Recent SAR studies on 4*H*-chromene derivatives **A** (UCPH-101), **B**, and **C** (SV30) (Fig. 1) reveal that they are potential inhibitors of EAAT1 (Excitatory amino acid transporters), anticancer agent and Bcl-2 inhibitor, respectively.[15] Also compounds **D** (HA 14-1) and **E** (Fig. 1) have potent biological activities.[1,15] Pyrano [2,3-*b*]pyridines and pyrano[2,3-*d*]pyrimidine derived from 2-amino-4*H*-chromenes possess antibacterial and fungicide activity.[16,17] Several 4*H*-chromene derivatives are useful as photoactive materials undergoing novel photochemical ring contraction to cyclobutenes from the triplet state.[6,18] Since the discovery of cromakalim as a typical ATP-sensitive potassium channel opener (PCO), a great number of 4*H*-chromene derivatives have been identified and verified to possess effective relaxant activity on blood vessels, cardiac muscle, and other smooth muscles.

Drugs having 4*H*-chromene moiety are being used in the treatment of a number of diseases, such as hypertension, asthma, ischemia, and urinary incontinence.[19–23] 4*H*-Chromene derivatives are administrated for treating a disorder responsive to the positive modulation of AMPA receptor in suffering animals.[24] The synthesis of 4*H*-chromenes by one-pot strategy has been reported using TMG-[bmim][X] and [2-aemim][PF_6] as catalyst[25,26] under microwave radiation. Only few reports exist in the literature in which organic catalysts, for example, tetrabutylammonium fluoride (TBAF), tetrabutylammonium bromide (TBABr), iodine, (*S*)-proline, iminium-allenamine, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), rare earth perfluorooctanoates, and hexadecyltrimethylammonium bromide have been employed for the synthesis of 4*H*-chromenes.[27–31,35c] The 4*H*-chromene moiety could also be designed by polymer-supported palladacycles with alkenes or allenes,[32] microwave-assisted liquid-phase,[33] and solid-phase like KF–alumina.[6,7,34] Because of their important use in pharmaceutical, great effort have been focussed toward developing new synthetic approaches for the construction of this privileged structure.

2. Results and discussion

As part of our continued interest to achieve high atom economic reactions, a multicomponent organic base mediated solvent free synthesis of medicinally promising ethyl 2-amino-3-cyano-4-(2-ethoxy-2-oxoethyl)-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-4-carboxylate derivatives (**4a**–**f**) under one-pot condition by the

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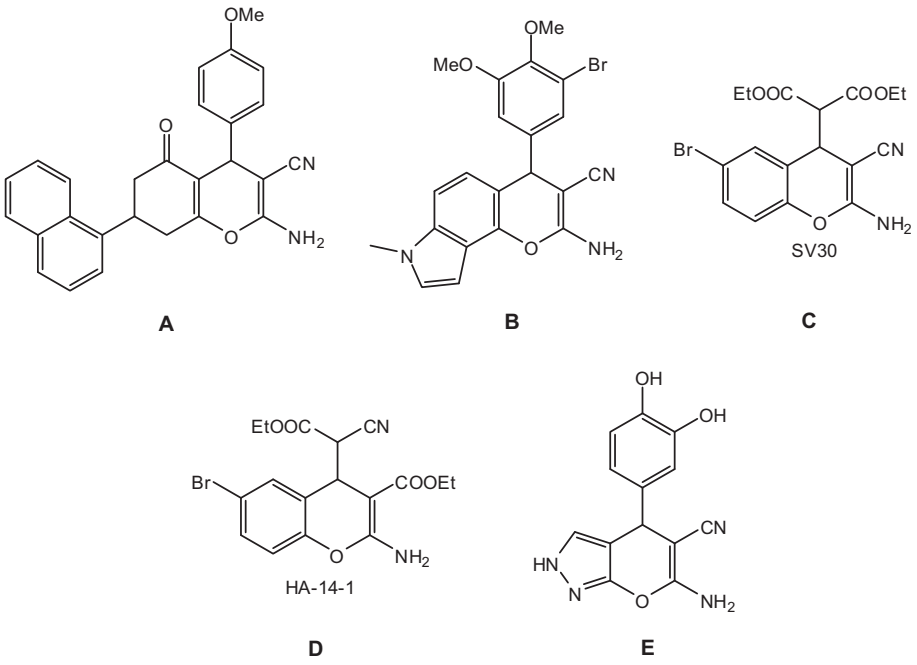


Fig. 1. Selected examples of 4*H*-chromenes with biological and pharmacological activity.

reaction of a variety of cyclohexane-1,3-diones (**1a**–**f**) with diethyl acetylenedicarboxylate (**2**) and malononitrile (**3**) has been developed. The reaction mixture was thoroughly ground with catalytic amount (0.3 equiv) of organic base at room temperature and then heated to 80 °C over a water bath. Rapid formation of 4*H*-chromene, yield ranging from 79 to 90% (Table 1), has been noticed within 30 min under the solvent free condition. All the synthesized 4*H*-chromene derivatives (**4a**–**f**) (Scheme 1) are unknown and completely characterized by spectral and single crystal X-ray analysis.

We speculate that the anion generated from the malononitrile (**3**) by methylamine attacks diethyl acetylenedicarboxylate to give Michael adduct **F**. The enolic form of cyclohexane-1,3-dione reacts with Michael adduct **F** leading to intermediate **G**. The migration of lone pair from oxygen leading to an intramolecular Michael addition–cyclization giving ultimately the 4*H*-chromene system (**4a**–**f**). The sequence of the reactions is presented in Scheme 2.

From the crystal structure (Fig. 2) (see the Supplementary data for more details, crystal data has CCDC number; CCDC-792844), it is clear that the methylene carbethoxy and carbethoxy groups are attached to C-4 of 4*H*-chromene system. The cyclohexenone ring has a half-chair/sofa conformation. The spectral data also supports the assigned structure.

The complete assignment of all hydrogens and carbons is possible with a set of two dimensional NMR experiments. Fig. 3 shows all the 2D connectivities between various carbon nuclei.

In the formation of **4b**, **4c**, and **4d**, the reaction is diastereoselective giving one diastereomer in each case. Though single crystal could not be grown for any of these compounds, the stereochemistry of these compounds can be assumed to the one in which the substituent at C-7 occupying an equatorial like orientation and is *cis* to the carbethoxy group at C-4 as in the crystal structure of **4f**. The influence of the organic base on the MCR-like transformation has been investigated in detail with **4f** and it is found that methylamine is the catalyst of choice. Triethylamine has also been found to be ideal, while other bases lead to relatively lower yields. These findings are summarized in Table 2. The optimized reaction time is 30 min at 80 °C.

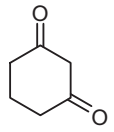
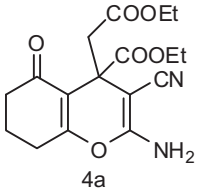
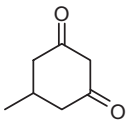
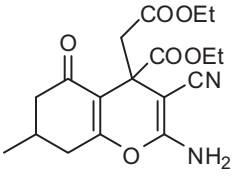
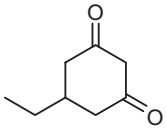
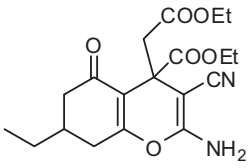
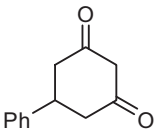
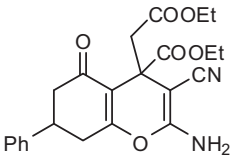
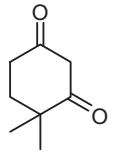
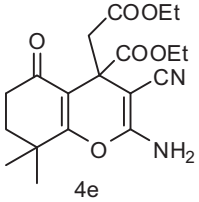
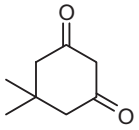
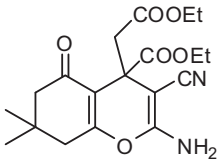
The same reaction has been carried out with 4-*tert*-butylcyclohexanone (**1g**), in the place of 1,3-diketone. Here again, the reaction went in the expected direction, but with low yield (42%). The product formed, ethyl 2-amino-6-*tert*-butyl-3-cyano-4-(2-ethoxy-2-oxoethyl)-5,6,7,8-tetrahydro-4*H*-chromene-4-carboxylate, (**5**; Scheme 3) has been confirmed by spectral data. This reaction shows that the presence of the second carbonyl group is not essential for 4*H*-chromenes formation, though the reaction course is definitely being influenced by the second carbonyl group.

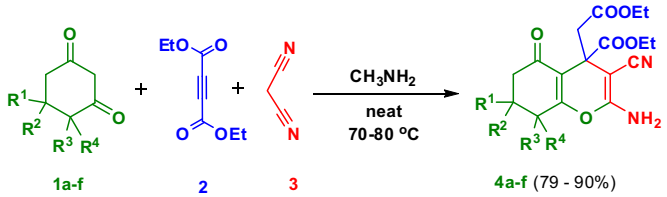
When the malononitrile component in the above reaction is replaced by other substrates with an active methylene (viz, ethyl cyanoacetate and ethyl bromoacetate), differently substituted 4*H*-chromene skeleton can be expected. Changing one of the component in classical reaction of this type is quite common and such a variation has led to variety of derivatives[35] like spiro[acenaphthylene-1,10-pyrano[2,3-*c*]pyrazolo-2-carbonitrile[36] derivatives. Spiro-oxindoles-4*H*-chromenes,[37] 2,3-dihydro-4*H*-chromene-4-ones, 2,3-dihydro-4-pyridinones,[38] bis(4*H*-chromene), 4*H*-benzo[*g*]chromene,[39] *N*-arylquinoline derivatives,[31] annulated 4*H*-chromenes,[40] dihydropyrano[4,3-*b*]pyranes,[41] and 4-ferrocenyl-4*H*-chromene[42] are all prepared by varying one of the component in classical 4*H*-chromene synthesis.

When ethyl cyanoacetate was used instead of malononitrile, the reaction proceeded smoothly yielding diethyl 2-amino-4-(2-ethoxy-2-oxoethyl)-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3,4-dicarboxylate, (**6**; Scheme 4). However, when ethyl bromoacetate was employed in the place of malononitrile, the course of the reaction is different and the expected 4*H*-chromenering is not generated. The product, obtained in trace amount, has been identified as 1,5-dimethyl pyrrolo[4,3,2-*de*]quinoline-2,4(1*H*,5*H*)-dione (**7**; Scheme 5) by spectral analysis.

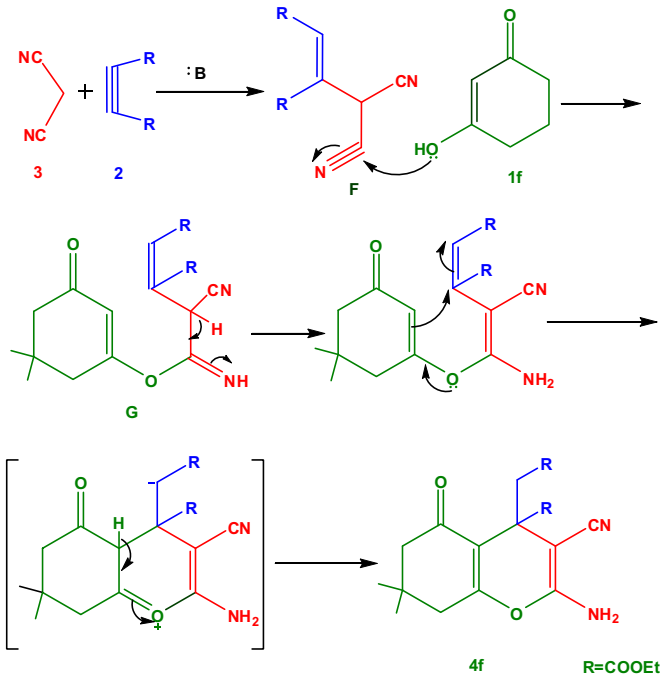
It has been found that **7** is not reported in literature, though this nucleus itself can be generated from indole derivatives.[43] From Scheme 5, it is clear that ethyl bromoacetate has not participated in the reaction; rather, the reaction is a multicomponent-like condensation involving methylamine. Indeed, a stoichiometric reaction of **1a** and **2** with methylamine delivers **7** in 68% yields. Unfortunately, when the reaction was carried out with other

Table 1
The isolated yield of 4*H*-chromene derivatives

Entry	Substrate	Product	Yield %
1		 4a	81
2		 4b	83
3		 4c	79
4		 4d	84
5		 4e	82
6		 4f	90



Scheme 1. Formation of 4*H*-chromene system (**4a**–**f**).



Scheme 2. Plausible mechanism for the formation of **4**.

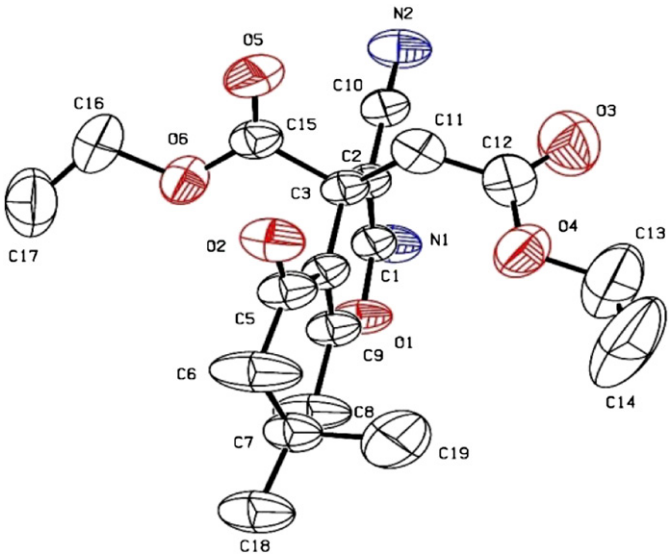


Fig. 2. ORTEP diagrams of **4f**.

primary amines, no fruitful result has been obtained. The reaction of dimedone, diethyl acetylenedicarboxylate, and methylamine has also not gone in the expected line with no conversion of the substrates even after considerable time. A possible explanation for the formation of **7** is depicted in Scheme 6.

We have also studied variation of the alkyne part of the three component reaction, replacing diethyl acetylenedicarboxylate with phenylacetylene. Here, it is not a multicomponent reaction, but a two component reaction with participation of methylamine yielding 5,5-dimethyl-3-(methylamino)cyclohex-2-enone[44] **8** in trace amount (Scheme 7). Clearly, the acetylenic carbon of phenyl acetylene is not electrophilic enough to undergo attack by the 1,3-diketone anion.

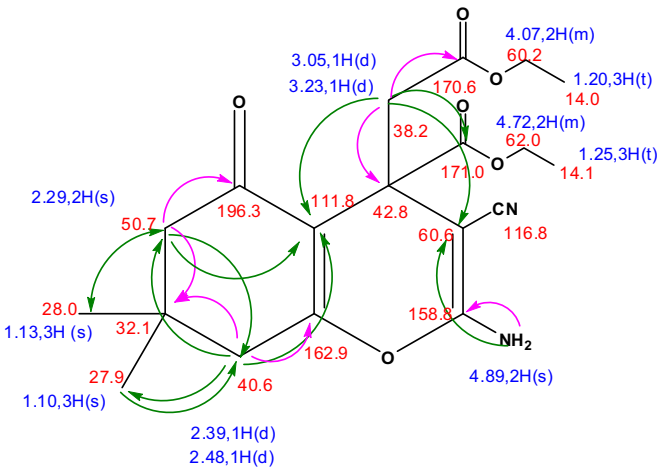
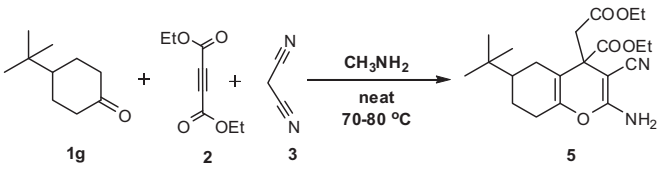


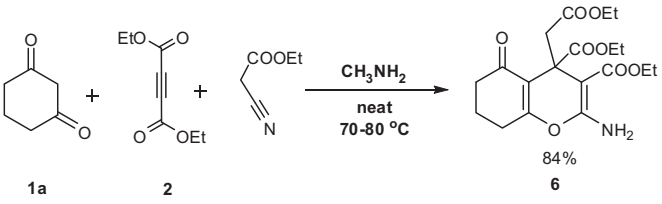
Fig. 3. HMBC correlation with ^{1}H and ^{13}C NMR of **4f** (Rose and green arrows show two and three bond connectivities, respectively).

Table 2
Screening of base on reaction for the preparation of **4f**

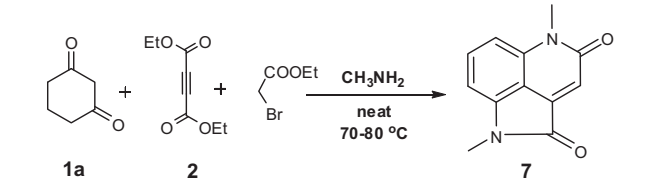
Entry	Base	Yield of **4f** (%)
1	Methylamine	90
2	Benzylamine	83
3	Triethylamine	88
4	Pyrrolidine	80
5	Piperidine	76
6	DBU	78
7	DABCO	74



Scheme 3. Reaction of **2** and **3** with **1g**.



Scheme 4. Reaction of **1a** and **2** with ethyl cyanoacetate.



Scheme 5. Formation of pyrroloquinoline-2,4-dione **7**.

When the 1,3-diketone taken is indane-1,3-dione, again the reaction is a not a multicomponent reaction, but a two component one yielding diethyl 4-oxo-4*H*-indeno[1,2-*b*]furan-2,3-dicarboxylate **9** (Scheme 8). The internal cyclization seems to be preferred to attack by the third component (Scheme 9). When the reaction was tested with cyclopentane-1,3-dione (**1i**) under the same conditions, the methylamine salt of diethyl 2-(2,5-dioxocyclopentyl)maleate (**10**) was obtained. In this case, cyclopentane-1,3-dione reacts with diethyl acetylenedicarboxylate (**2**) to form 2-(2,5-dioxocyclopentyl) maleate and the subsequent removal of second hydrogen leads to carbanion forming an ammonium salt with methylamine (Scheme 10). This stable carbanion is reluctant to undergo further reaction as in the case of Scheme 9.

With a linear 1,3-diketone like acetylacetone, diethyl acetylene dicarboxylate is not incorporated to generate the 4*H*-chromene system. Rather only dihydropyridine **11**[45,46] (Scheme 11) has been obtained in trace. While using the calculated moles of methylamine, we got 76% of **11**.

3. Conclusion

In summary, an atom economic method for the synthesis of highly substituted 4*H*-chromene derivatives in high yield has been developed. This is the first report to generate 4*H*-chromene from acetylene precursors. The reaction condition has been optimized with different bases. The final products have many reactive sites and may serve as useful synthons to construct additional rings. The scope of the reaction has been explored by varying the different components of this multicomponent reaction and the results have been summarized.

4. Experimental section

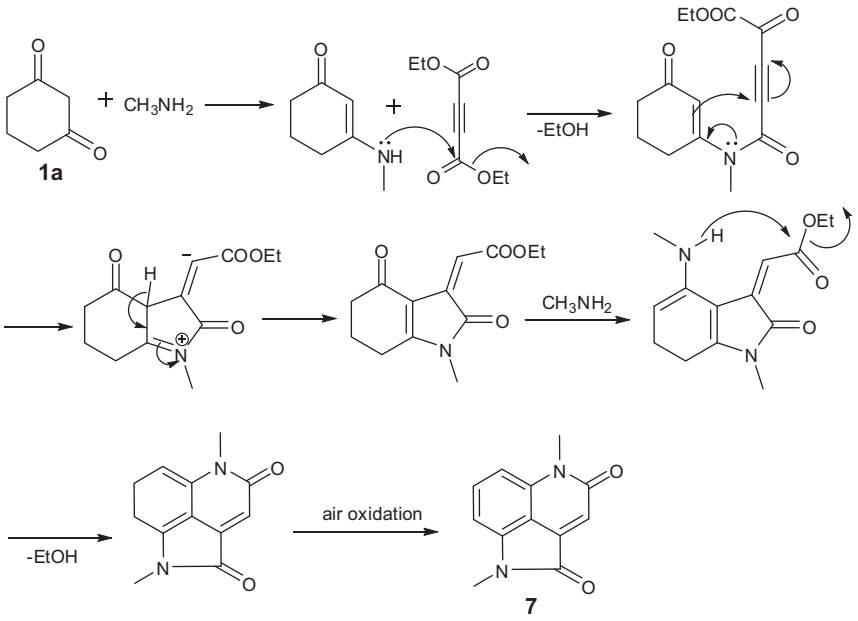
4.1. General

Melting points were measured in open capillary tubes and are uncorrected. The ^{1}H NMR, ^{13}C NMR, DEPT, H,H-COSY, C,H-COSY, and HMBC spectra were recorded on a Bruker (Avance) 300 MHz NMR instrument using TMS as internal standard and DMSO-d_6 as solvent. Standard Bruker software was used throughout. Chemical shifts are given in parts per million (δ scale) and the coupling constants are given in Hertz. Infrared spectra were recorded on an SHIMADZU FT IR instrument (in KBr pellet). Band positions are reported in reciprocal centimeters (cm^{-1}). Silica gel-G plates (Merck) were used for TLC analysis with a mixture of petroleum ether (60–80 °C) and ethyl acetate as eluent. Elemental analyses were performed on a Perkin–Elmer 2400 Series II Elemental CHNS analyzer.

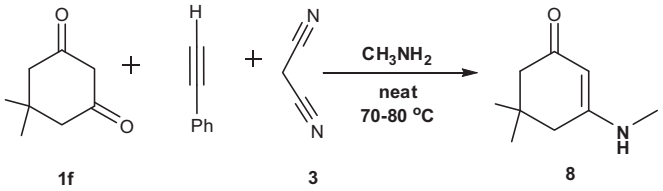
4.2. General procedure for the synthesis of ethyl 2-amino-3-cyano-4-(2-ethoxy-2-oxoethyl)-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-4-carboxylate derivatives (4)

To a mixture of cyclic 1,3-dione (7.1 mmol), diethyl acetylene dicarboxylate (7.1 mmol), and malononitrile (7.1 mmol) was added methylamine (2.1 mmol) dropwise at room temperature. The reaction mixture was thoroughly ground and heated to 80 °C for 30 min. Then molten mass was allowed to cool to room temperature and the resulting mixture was poured into water and the product was extracted with a minimum amount of chloroform, dried over sodium sulfate and crystallized in 3:2 chloroform/ethyl acetate to yield pure derivative of ethyl 2-amino-3-cyano-4-(2-ethoxy-2-oxoethyl)-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-4-carboxylate (**4**). Spectroscopic data for all the compounds are given below.

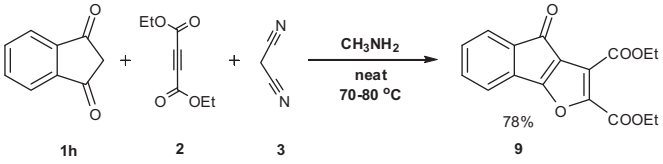
*4.2.1. Ethyl 2-amino-3-cyano-4-(2-ethoxy-2-oxoethyl)-5-oxo-5,6,7,8-tetrahydro-4H-chromene-4-carboxylate (**4a**).* The title compound was prepared according to general procedure in Section 4.2 using cyclohexane-1,3-dione. The resulting mixture was poured into



Scheme 6. Proposed mechanism for the formation of **7**.



Scheme 7. Reaction of **1f** and **3** with phenyl acetylene.

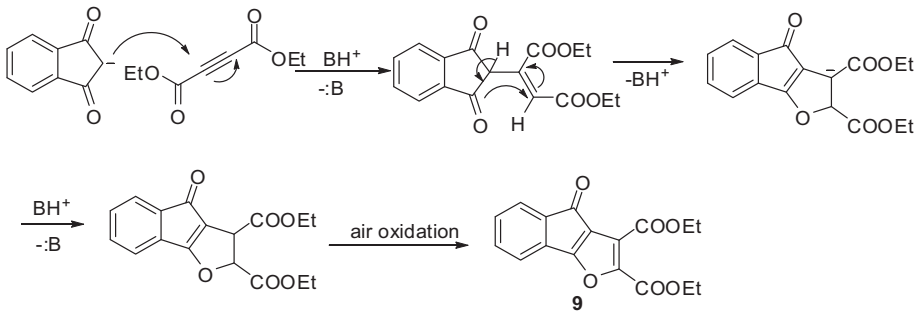


Scheme 8. Reaction of indane-1,3-dione with **2** and **3**.

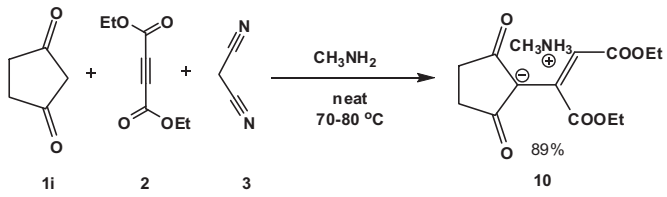
water and the product was extracted with a minimum amount of chloroform, dried over sodium sulfate and the crude product was purified by crystallization in 3:2 chloroform/ethyl acetate as colorless solid; mp 118–120 °C; [Found: C, 58.57; H, 5.77; N, 8.01, $C_{17}H_{20}N_2O_6$ requires C, 58.61; H, 5.79; N, 8.04]; IR (KBr, pellet) 3325, 3199, 2966, 1735 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.21 (3H, t, J=3.6 Hz, CH_3), 1.25 (3H, t, J=5.7 Hz, CH_3), 2.23 (2H, m, CH_2), 2.43 (2H, m, CH_2), 2.58 (2H, t, J=6 Hz, CH_2), 3.05 (1H, d, J=16.2 Hz, CH_aH_bCOOEt), 3.18 (1H, d, J=15.9 Hz, CH_bH_aCOOEt), 4.07 (2H, m, CH_2), 4.17 (2H, m, CH_2), 5.15 (2H, s, NH_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.9, 14.0, 19.9, 26.9, 36.7, 38.5, 42.9, 59.9, 60.2, 62.0, 112.8, 116.8, 158.8, 164.6, 170.5, 171.2, 196.2; m/z (ES^+) ($[M+H]^+$) found 349.4. $C_{17}H_{20}N_2O_6$ requires 348.1.

*4.2.2. Ethyl 2-amino-3-cyano-4-(2-ethoxy-2-oxoethyl)-7-methyl-5-oxo-5,6,7,8-tetrahydro-4H-chromene-4-carboxylate (**4b**).* The title compound was prepared according to general procedure in Section 4.2 using 5-methylcyclohexane-1,3-dione. The resulting mixture was poured into water and the product was extracted with a minimum amount of chloroform, dried over sodium sulfate and the crude product was purified by crystallization in 3:2 chloroform/ethyl acetate as colorless solid; mp 178–180 °C; [Found: C, 59.62; H, 6.10; N, 7.68, $C_{18}H_{22}N_2O_6$ requires C, 59.66; H, 6.12; N, 7.73]; IR (KBr, pellet) 3373, 3203, 2981, 1724 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.11 (3H, m, $CHCH_3$), 1.23 (6H, m, 2× CH_3), 2.21 (1H, m, $CHCH_3$), 2.32 (2H, m, CH_2), 2.53 (2H, m, CH_2), 3.06 (1H, d, J=16.2 Hz, CH_aH_bCOOEt), 3.18 (1H, d, J=15.9 Hz, CH_bH_aCOOEt), 4.07 (2H, m, CH_2), 4.18 (2H, m, CH_2), 5.04 (2H, s, NH_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.9, 14.0, 20.3, 27.6, 34.9, 38.2, 38.6, 44.8, 60.2, 60.4, 62.0, 112.5, 116.8, 158.8, 163.9, 170.5, 171.1, 196.1.

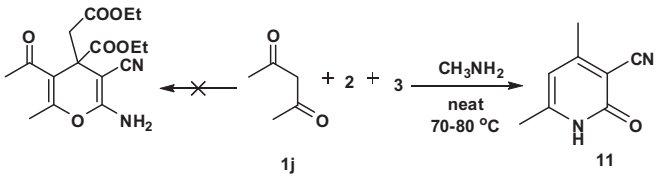
*4.2.3. Ethyl 2-amino-3-cyano-4-(2-ethoxy-2-oxoethyl)-7-ethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromene-4-carboxylate (**4c**).* The title



Scheme 9. Proposed mechanism for the formation of **9**.



Scheme 10. Reaction with cyclopentane-1,3-dione (**1i**).



Scheme 11. Formation of dihydropyridine **11**.

compound was prepared according to general procedure in Section 4.2 using 5-ethylcyclohexane-1,3-dione. The resulting mixture was poured into water and the product was extracted with a minimum amount of chloroform, dried over sodium sulfate and the crude product was purified by crystallization in 3:2 chloroform/ethyl acetate as colorless solid; mp 120–122 °C; [Found: C, 60.59; H, 6.40; N, 7.41.$C_{19}H_{24}N_2O_6$ requires C, 60.63; H, 6.43; N, 7.44]; IR (KBr, pellet) 3375, 3249, 2981, 1734 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.94 (3H, t, J=7.3 Hz, CH_3), 1.27 (6H, m, 2× CH_3), 1.46 (2H, m, CH_2), 2.14 (2H, m, CH_2), 2.36 (1H, m, CH), 2.53 (2H m, CH_2), 3.08 (1H, d, J=16.2 Hz, CH_aH_bCOOEt), 3.19 (1H, d, J=16.2 Hz, CH_bH_aCOOEt), 4.06 (2H, m, CH_2), 4.18 (2H, m, CH_2), 4.91 (2H, s, NH_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.2, 14.3, 14.5, 28.2, 30.0, 34.5, 34.6, 39.0, 43.3, 60.6, 61.6, 62.4, 113.2, 117.0, 159.1, 164.4, 170.9, 171.4, 196.4.

*4.2.4. Ethyl 2-amino-3-cyano-4-(2-ethoxy-2-oxoethyl)-5-oxo-7-phenyl-5,6,7,8-tetrahydro-4H-chromene-4-carboxylate (**4d**).* The title compound was prepared according to general procedure in Section 4.2 using 5-phenylcyclohexane-1,3-dione. The resulting mixture was poured into water and the product was extracted with a minimum amount of chloroform, dried over sodium sulfate and the crude product was purified by crystallization in 3:2 chloroform/ethyl acetate as colorless solid; mp 137–139 °C; [Found: C, 65.03; H, 5.67; N, 6.58. $C_{23}H_{24}N_2O_6$requires C, 65.08; H, 5.70; N, 6.60]; IR (KBr, pellet) 3392, 3213, 2981, 1725 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.24 (6H, m, 2× CH_3), 2.27 (4H, m, 2× CH_2), 3.12 (1H, d, J=16.2 Hz, CH_aH_bCOOEt), 3.20 (1H, d, J=16.2 Hz, CH_bH_aCOOEt), 3.40 (1H, m, CH), 4.09 (2H, m, CH_2), 4.18 (2H, m, CH_2), 4.97 (2H, s, NH_2), 7.31 (5H, m, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.9, 14.0, 34.4, 37.9, 38.6, 43.0, 43,7, 60.2, 60.4, 62.1, 112.7, 116.6, 126.5*, 127.3, 128.8*, 141.5, 158.8, 163.8, 170.5, 171.0, 195.2.

*4.2.5. Ethyl 2-amino-3-cyano-4-(2-ethoxy-2-oxoethyl)-8,8-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromene-4-carboxylate (**4e**).* The title compound was prepared according to general procedure in Section 4.2 using 4,4-dimethylcyclohexane-1,3-dione. The resulting mixture was poured into water and the product was extracted with a minimum amount of chloroform, dried over sodium sulfate and the crude product was purified by crystallization in 3:2 chloroform/ethyl acetate as colorless solid; mp 238–240 °C; [Found: C, 60.61; H, 6.38; N, 7.39. $C_{19}H_{24}N_2O_6$ requires C, 60.63; H, 6.43; N, 7.44]; IR (KBr, pellet) 3365, 3319, 2970, 1729 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.10 (3H, s, CH_3), 1.11 (3H, s, CH_3), 1.23 (6H, m, 2× CH_3), 1.86 (2H, t, J=6.4 Hz, CH_2), 2.58 (2H, t, J=6.4 Hz, CH_2), 3.05 (1H, d, J=15.9 Hz, CH_aH_bCOOEt), 3.16 (1H, d, J=16.2 Hz, CH_bH_aCOOEt), 4.07 (2H, m, CH_2), 4.20 (2H, m, CH_2), 5.05 (2H, s, NH_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.9, 14.0, 23.7, 24.1*, 33.3, 38.6, 40.5, 43.2, 60.1, 60.4, 61.8, 111.1, 116.8, 158.8, 162.6, 170.6, 171.1, 200.9.

*4.2.6. Ethyl 2-amino-3-cyano-4-(2-ethoxy-2-oxoethyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromene-4-carboxylate (**4f**).* The title compound was prepared according to general procedure in Section 4.2 using 5,5-dimethylcyclohexane-1,3-dione. The resulting mixture was poured into water and the product was extracted with a minimum amount of chloroform, dried over sodium sulfate and the crude product was purified by crystallization in 3:2 chloroform/ethyl acetate as colorless solid; mp 238–239 °C; [Found: C, 60.57; H, 6.39; N, 7.40. $C_{19}H_{24}N_2O_6$ requires C, 60.63; H, 6.43; N, 7.44]; IR (KBr, pellet) 3319, 3253, 2970, 1732 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.10 (3H, s, CH_3), 1.13 (3H, s, CH_3), 1.20 (3H, t, J=6.6 Hz, CH_3), 1.25 (3H, t, J=6.4 Hz, CH_3), 2.29 (2H, s, CH_2), 2.39 (1H, d, J=17.7 Hz, CH_aH_b), 2.48 (1H, d, J=17.7 Hz, CH_bH_a), 3.09 (1H, d, J=16.5 Hz, CH_aH_bCOOEt), 3.23 (1H, d, J=16.5 Hz, CH_aH_bCOOEt), 4.07 (2H, m, CH_2), 4.20 (2H, m, CH_2), 4.72 (2H, s, NH_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.0, 14.1, 27.9, 28.0, 32.1, 38.2, 40.6, 42.8, 50.7, 60.2, 60.6, 62.0, 111.8, 116.8, 158.8, 162.9, 170.6, 171.0, 196.3; m/z (ES^+) ($[M+H]^+$) found 377.4. $C_{19}H_{24}N_2O_6$ requires 376.1.

*4.2.7. Ethyl 2-amino-6-tert-butyl-3-cyano-4-(2-ethoxy-2-oxoethyl)-5,6,7,8-tetrahydro-4H-chromene-4-carboxylate (**5**).* The title compound was prepared according to general procedure in Section 4.2 using 4-*tert*-butylcyclohexanone. The resulting mixture was poured into water and the product was extracted with a minimum amount of chloroform, dried over sodium sulfate and the crude product was purified by crystallization in 3:2 chloroform/ethyl acetate as colorless solid; mp 156–158 °C; IR (KBr, pellet) 3365, 3180, 2970, 1718 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.85 (9H, s, 3× CH_3), 1.30 (6H, m, 2× CH_3), 1.70–2.45 (m, 7H, 3× CH_2, CH), 2.95 (1H, d, J=15.9 Hz, CH_aH_bCOOEt), 3.42 (1H, d, J=15.9 Hz, CH_bH_aCOOEt), 4.25 (4H, m, 2× CH_2), 5.50 (2H, s, NH_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.6, 13.7, 22.7, 26.9*, 27.6, 28.9, 32.2, 36.7, 44.4, 55.1, 61.6, 62.7, 62.9, 115.0, 120.5, 127.9, 144.1, 166.5, 168.2.

*4.2.8. Diethyl 2-amino-4-(2-ethoxy-2-oxoethyl)-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3,4-dicarboxylate (**6**).* The title compound was prepared according to general procedure in Section 4.2 using cyclohexane-1,3-dione. The resulting mixture was poured into water and the product was extracted with a minimum amount of chloroform, dried over sodium sulfate and the crude product was purified by crystallization in 3:2 chloroform/ethyl acetate as colorless solid; yield 84%; mp 127–129 °C; [Found: C, 57.67; H, 6.33; N, 3.45. $C_{19}H_{25}NO_8$ requires C, 57.71; H, 6.37; N, 3.54]; IR (KBr, pellet) 3373, 3230, 2983, 1730 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.17 (3H, t, J=6.3 Hz, CH_3), 1.27 (6H, m, 2× CH_3), 2.01 (2H, m, CH_2), 2.40 (2H, m, CH_2), 2.55 (2H, t, J=6.3 Hz, CH_2), 3.05 (1H, d, J=15.3 Hz, CH_aH_bCOOEt), 3.25 (1H, d, J=15.3 Hz, CH_bH_aCOOEt), 4.14 (6H, m, 3× CH_2), 6.54 (2H, s, NH_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.8, 14.2*, 19.8, 27.2, 37.3, 39.0, 43.6, 59.6, 59.8, 61.0, 78.4, 115.3, 158.8, 164.1, 168.2, 171.5, 173.5, 196.2.

*4.2.9. 1,5-Dimethylpyrrolo[4,3,2-de]quinoline-2,4(1H,5H)-dione (**7**).* The title compound was obtained by the general procedure in Section 4.2 using cyclohexane-1,3-dione. The resulting mixture was poured into water and the product was extracted with a minimum amount of chloroform, dried over sodium sulfate and the crude product was purified by crystallization in 3:2 chloroform/ethyl acetate as colorless solid; mp 212–214 °C; [Found: C, 67.24; H, 4.68; N, 13.05. $C_{12}H_{10}N_2O_2$ requires C, 67.28; H, 4.71; N, 13.08]; IR (KBr, pellet) 3137, 3230, 2939, 1728 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.34 (3H, s, NCH_3), 3.68 (3H, s, NCH_3), 6.65 (1H, d, J=8.4 Hz, ArH),

6.95 (1H, d, J=8.4 Hz, ArH), 7.14 (1H, s, CH), 7.51 (1H, t, J=8.4 Hz, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.6, 29.6, 102.2, 107.9, 108.9, 119.3, 133.5, 136.7, 137.1, 141.4, 163.8, 165.7.

*4.2.10. 5,5-Dimethyl-3-(methylamino)cyclohex-2-enone (**8**).* White solid; mp 154–156 °C (lit. 153–154 °C);[44] ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.06 (6H, s, 2× CH_3), 2.17 (2H, s, CH_2), 2.21 (2H, s, CH_2), 2.80 (3H, d, J=4.5 Hz, NCH_3), 5.07 (1H, s, CH), 5.67 (1H, s, NH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.2*, 29.5, 32.7, 43.2, 50.2, 94.8, 164.3, 196.7.

*4.2.11. Diethyl 4-oxo-4H-indeno[1,2-b]furan-2,3-dicarboxylate (**9**).* The title compound was obtained by the general procedure in Section 4.2 using cyclohexane-1,3-dione. The resulting mixture was poured into water and the product was extracted with a minimum amount of chloroform, dried over sodium sulfate and the crude product was purified by crystallization in 3:2 chloroform/ethyl acetate as colorless solid; yield 78%; mp 157–159 °C; [Found: C, 64.94; H, 4.45. $C_{17}H_{14}O_6$ requires C, 64.97; H, 4.49]; IR (KBr, pellet) 3421, 1749, 1706, 1687, 1429 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.35 (3H, t, J=7.2 Hz, CH_3), 1.44 (3H, t, J=7.2 Hz, CH_3), 4.35 (2H, q, J=7.2 Hz, CH_2), 4.51 (2H, q, J=7.2 Hz, CH_2), 7.49 (1H, t, J=7.5 Hz, ArH), 7.59 (1H, t, J=7.5 Hz, ArH), 7.70 (1H, d, J=7.5 Hz, ArH), 8.18 (1H, d, J=7.5 Hz, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.7, 13.8, 62.0, 62.1, 106.1, 114.6, 119.1, 122.9, 124.1, 132.1, 134.5, 135.7, 138.9, 151.3, 156.2, 165.8, 187.5.

*4.2.12. Methanaminium 1-(1,4-diethoxy-1,4-dioxobut-2-en-2-yl)-2,5-dioxocyclopentan-1-ide (**10**).* Yield 89%; white solid; ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.30 (6H, m, CH_3), 2.17 (4H, s, 2× CH_2), 2.49 (3H, s, CH_3), 4.04 (2H, q, CH_2), 4.21 (2H, q, CH_2), 6.97 (1H, s, CH), 7.69 (3H, s, NH_3); ^{13}C NMR (75 MHz, DMSO-d_6) δ 14.2, 14.7, 23.9, 33.9, 58.6, 59.5, 100.7, 105.6, 145.4, 167.6, 169.0, 199.4.

*4.2.13. 4,6-Dimethyl-2-oxo-1,2-dihydropyridine-3-carbonitrile (**11**).* White solid; mp 287–289 °C (lit. 285–286 °C);[45,46] ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.29 (3H, s, CH_3), 2.37 (3H, s, CH_3), 6.03 (1H, s, CH); ^{13}C NMR (75 MHz, DMSO-d_6) δ 18.1, 19.8, 99.0, 106.7, 114.6, 149.5, 159.1, 160.6.

*One carbon has merged with other.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2011.06.021.

References and notes

1. (a) Dong, Z. H.; Liu, X. H.; Feng, J. H.; Wang, M.; Lin, L. L.; Fen, X. M. *Eur. J. Org. Chem.* **2011**, 137; (b) Schmidt, E. Y.; Trofimov, B. A.; Zorina, N. V.; Mikhaleva, A. I.; Ushakov, I. A.; Skital'tseva, E. V.; Kazheva, O. N.; Alexandrov, G. G.; Dyachenko, O. A. *Eur. J. Org. Chem.* **2010**, 6727; (c) Moon, D.; Kim, M.; Kang, S.; Choi, Y.; Park, S.; Kim, G. *Cancer Lett.* **2010**, *292*, 111; (d) Hatakeyama, S.; Ochi, N.; Numata, H.; Takano, S. *J. Chem. Soc., Chem. Commun.* **1988**, *17*, 1202; (e) Moafi, L.; Ahadi, S.; Bazgir, A. *Tetrahedron Lett.* **2010**, *51*, 6270.
2. (a) Yao, C.; Jiang, B.; Li, T.; Qin, B.; Feng, X.; Zhang, H.; Wang, C.; Tu, S. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 599; (b) Gonzalez, R.; Martin, N.; Seoane, C.; Marco, J. L.; Albert, A.; Cano, F. H. *Tetrahedron Lett.* **1992**, *33*, 3809; (c) Gonzalez, R.; Martin, N.; Seoane, C.; Soto, J. *J. Chem. Soc., Perkin Trans. 1* **1985**, 202.
3. (a) Sabry, N. M.; Mohamed, H. M.; Khattab, E. S. A. E. H.; Motlaq, S. S.; El-Agrody, A. M. *Eur. J. Med. Chem.* **2011**, *46*, 765; (b) Costa, M.; Proença, F. *Tetrahedron* **2011**, *67*, 1799; (c) Elinson, M. N.; Ilovaisky, A. I.; Merkulova, V. M.; Belyakov, P. A.; Chizhov, A. O.; Nikishin, G. I. *Tetrahedron* **2010**, *66*, 4043; (d) Green, G. R.; Evans, J. M.; Vong, A. K. In *Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R., Rees, C. W., Scriven, E. F. V., Eds.; Pergamon: Oxford, 1995; Vol. 5, p 469.
4. (a) Murthy, S. N.; Madhav, B.; Reddy, V. P.; Nageswar, Y. V. D. *Tetrahedron Lett.* **2010**, *51*, 3649; (b) Ding, D.; Zhao, C. G. *Tetrahedron Lett.* **2010**, *51*, 1322; (c) Foye, W. O. *Prinicipi di Chimica Farmaceutica*; Piccin: Padova, Italy, 1991; p 416; (d) Adreani, L. L.; Lapi, E. *Boll. Chim. Farm.* **1960**, *99*, 583; *Chem. Abstr.* **1961**, *55*, 2668d.
5. (a) Bonacorso, H. G.; Navarini, J.; Wiethan, C. W.; Bortolotto, G. P.; Paima, G. R.; Cavinatto, S.; Martins, M. A. P.; Zanatta, N.; Caro, M. S. B. *J. Fluorine Chem.* **2011**, *132*, 160; (b) Zhang, Y. L.; Chen, B. Z.; Zheng, K. Q.; Xu, M. L.; Lei, X. H. *Yao Xue Xue Bao* **1982**, *17*, 17; *Chem. Abstr.* **1982**, *96*, 135383e.
6. Babu, N. S.; Pasha, N.; Rao, K. T. V.; Prasad, P. S. S.; Lingaiah, N. *Tetrahedron Lett.* **2008**, *49*, 2730.
7. Devi, I.; Bhuyan, P. J. *Tetrahedron Lett.* **2004**, *45*, 8625.
8. (a) Bonsignore, L.; Loy, G.; Secci, D.; Calignano, A. *Eur. J. Med. Chem.* **1993**, *28*, 517; (b) Witte, E. C.; Neubert, P.; Roesch, A. Ger. Offen. DE, 1986, 3427985; *Chem. Abstr.* **1986**, *104*, 224915f.
9. Ellis, G. P. The chemistry of heterocyclic compounds In *Chromene, Chromanes and Chromone*; Weissberger, A., Taylor, E. C., Eds.; John Wiley: New York, NY, 1977; p 13.
10. (a) Jin, T. S.; Liu, L. B.; Zhao, Y.; Li, T. S. *Synth. Commun.* **2005**, *35*, 2379; (b) Abdel Galil, F. M.; Riad, B. Y.; Sherif, S. M.; Elnagdi, M. H. *Chem. Lett.* **1982**, 1123.
11. (a) Morinaka Y.; Takahashi, K. Jpn. Patent, JP52017498, 1977; (b) Hafez, E. A.; Elnagdi, M. H.; Elagamey, A. A.; El-Taweel, F. A. *Heterocycles* **1987**, *26*, 903.
12. (a) Abdelrazeka, F. M.; Metza, P.; Farragb, E. K. *Arch. Pharm. Pharm. Med. Chem.* **2004**, *337*, 482; (b) El-Rahmana, N. M. A.; El-Kateba, A. A.; Mady, M. F. *Synth. Commun.* **2007**, *37*, 3961; (c) Darbarwar, M.; Sundarmurthy, V. *Synthesis* **1982**, 337.
13. Ghosal, S.; Murugandam, V.; Mukhopadhyay, B.; Bhattacharya, S. *Indian J. Chem.* **1997**, *36B*, 59.
14. O'Callaghan, C. N.; McMurry, T. B. H. *J. Chem. Res.* **1995**, 214.
15. (a) Erichsen, M. N.; Huynh, T. H. V.; Abrahamsen, B.; Bastlund, J. F.; Bundgaard, C.; Monrad, O.; Jensen, A. B.; Nielsen, C. W.; Frydenvang, K.; Jensen, A. A.; Bunch, L. *J. Med. Chem.* **2010**, *53*, 7180; (b) Kemnitzer, W.; Drewe, J.; Jiang, S.; Zhang, H.; Grundy, C. C.; Labreque, D.; Bubenick, M.; Attardo, G.; Denis, R.; Lamothe, S.; Gourdeau, H.; Tseng, B.; Kasibhatla, S.; Cai, S. X. *J. Med. Chem.* **2008**, *51*, 417; (c) Mahmoodi, M.; Aliabadi, A.; Emami, S.; Safavi, M.; Rajabalian, S.; AliMohagheghi, M.; Khoshzaban, A.; Kermani, A. S.; Lamei, N.; Shafiee, A.; Foroumadi, A. *Arch. Pharm. Chem. Life Sci.* **2010**, *343*, 411; (d) Doshi, J. M.; Tian, D.; Xing, C. *J. Med. Chem.* **2006**, *49*, 7731.
16. Selvam, N. P.; Babu, T. H.; Perumal, P. T. *Tetrahedron* **2009**, *65*, 8524.
17. (a) Bedair, A. H.; Emam, H. A.; El-Hady, N. A.; Ahmed, K. A. R.; El-Agrody, A. M. *Farmaco* **2001**, *56*, 965; (b) Khafagy, M. M.; El-Wahab, A. H. F. A.; Eid, F. A.; El-Agrody, A. M. *Farmaco* **2002**, *57*, 715; (c) Eid, F. A.; El-Wahab, A. H. F. A.; Gameel, A. M. E. H. A.; Khafagy, M. A. M. *Acta Pharm.* **2004**, *54*, 13.
18. (a) Gaplovsky, A.; Donovalova, J.; Lacova, M.; Mracnova, R.; El-Shaaer, H. M. *J. Photochem. Photobiol., A* **2000**, *61*, 136; (b) Armesto, D.; Horspool, W. M.; Martin, N.; Ramos, A.; Seoane, C. *J. Org. Chem.* **1989**, *54*, 3069.
19. Shia, D.; Moua, J.; Zhuanga, Q.; Wanga, X. *J. Chem. Res.* **2004**, 821.
20. Poyser, R. H.; Hamilton, T. C. *Drugs Future* **1994**, *19*, 39.
21. Empfield, J. R.; Russell, K. *Annu. Rep. Med. Chem.* **1996**, *30*, 81.
22. Pirotte, B.; Fontaine, J.; Lebrun, P. *Curr. Med. Chem.* **1995**, *2*, 573.
23. Atwal, K. S. *Curr. Med. Chem.* **1996**, *3*, 27.
24. Konkoy, C. S.; Fick, D. B.; Cai, S. X.; Lan, N. C.; Keana, J. F. W. U.S. Patent 6,680,332 B1, 2004.
25. Zhou, J. F.; Tu, S. J.; Gao, Y.; Ji, M. *Chin. J. Org. Chem.* **2001**, *21*, 742.
26. Peng, Y.; Song, G. *Catal. Commun.* **2007**, *8*, 111.
27. (a) Jereba, M.; Vrazic, D.; Zupana, M. *Tetrahedron* **2011**, *67*, 1355; (b) Fotouhi, L.; Heravi, M. M.; Fatehi, A.; Bakhtiari, K. *Tetrahedron Lett.* **2007**, *48*, 5379.
28. (a) Jin, T. S.; Xiao, J. C.; Wang, S. J.; Li, T. S.; Song, X. R. *Synlett* **2003**, 2001; (b) Ranu, B. C.; Banerjee, S.; Roy, S. *Indian J. Chem.* **2008**, *47B*, 1108; (c) Pasha, M. A.; Jayashankara, V. P. *Indian J. Chem.* **2007**, *46B*, 1328; (d) Tripathi, A. K.; Koul, S.; Taneja, S. C. *Indian J. Chem.* **2010**, *49B*, 1561.
29. (a) Balalaie, S.; Bararjanian, M.; Amani, A. M.; Movassagh, B. *Synlett* **2006**, 263; (b) Dyachenko, V. D.; Chernega, A. N. *Russ. J. Org. Chem.* **2006**, *42*, 567.
30. (a) Jin, T. S.; Wang, A. Q.; Wang, X.; Zhang, J. S.; Li, T. S. *Synlett* **2004**, 871; (b) Das, B.; Krishnaiah, M.; Laxminarayana, K.; Damodar, K.; Nandan Kumar, D. *Chem. Lett.* **2008**, *37*, 1000; (c) Mashraqui, S. H.; Patil, M. B.; Mistry, H. D.; Ghadigaonkar, S.; Meetsma, A. *Chem. Lett.* **2008**, *37*, 1000.
31. (a) Gao, S.; Tsai, C. H.; Tseng, C.; Yao, C. F. *Tetrahedron* **2008**, *64*, 9143; (b) Hekmatshore, R.; Majedi, S.; Bakhtiari, K. *Catal. Commun.* **2008**, *9*, 307; (c) Jamal, M. R. N.; Mashkouri, S.; Sharif, A. *Mol. Diversity* **2010**, *14*, 473.
32. Hershberger, J. C.; Zhang, L.; Lu, G.; Malinakova, H. C. *J. Org. Chem.* **2006**, *71*, 231.
33. (a) Yi, F.; Peng, Y.; Song, G. *Tetrahedron Lett.* **2005**, *46*, 3931; (b) Nicola, T.; Vieser, R.; Eberbach, W. *Eur. J. Org. Chem.* **2000**, 527.
34. (a) Kumar, D.; Reddy, V. B.; Sharad, S.; Dube, U.; Kapur, S. *Eur. J. Med. Chem.* **2009**, *44*, 3805; (b) Wang, X. S.; Shi, D. Q.; Tu, S. J.; Yao, C. S. *Synth. Commun.* **2003**, *33*, 119.
35. (a) Kumaravel, K.; Vasuki, G. *Green Chem.* **2009**, *11*, 1945; (b) Fan, J.; Wang, Z. *Chem. Commun.* **2008**, 5381; (c) Liu, C.; Zhang, X.; Wang, R.; Wang, W. *Org. Lett.* **2010**, *12*, 4948; (d) Ye, L.-W.; Sun, X.-L.; Zhu, C.-Y.; Tang, Y. *Org. Lett.* **2010**, *12*, 4948; (e) Yavari, I.; Adib, M.; Sayahi, M. H. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2343; (f) Maghsoodlou, M. T.; Yavari, I.; Nassiri, F.; Djahaniani, H.; Razmjoo, Z. *Monatsh. Chem.* **2003**, *12*, 1585; (g) Teimouri, M. B.; Bazhrang, R. *Monatsh. Chem.* **2009**, *5*, 513; (h) Bayat, M.; Shiraz, N. Z.; Asayesh, S. S. *J. Heterocycl. Chem.* **2010**, *47*, 857.
36. Saeedi, M.; Heravi, M. M.; Beheshtiha, Y. S.; Oskooie, H. A. *Tetrahedron* **2010**, *66*, 5345.

37. Elinson, M. N.; Ilovaisky, A. I.; Dorofeev, A. S.; Merkulova, V. M.; Stepanov, N. O.; Miloserdov, F. M.; Ogibin, Y. N.; Nikishin, G. I. *Tetrahedron* **2007**, *63*, 10543.
38. MacDonald, F. K.; Burnell, D. J. *J. Org. Chem.* **2009**, *74*, 6973.
39. Shaabani, A.; Ghadari, R.; Sarvary, A.; Rezayan, A. H. *J. Org. Chem.* **2009**, *74*, 4372.
40. Teimouri, M. B.; Bazhrang, R.; Eslamimanesha, V.; Nouri, A. *Tetrahedron* **2006**, *62*, 3016.
41. Khurana, J. M.; Nand, B.; Saluja, P. *Tetrahedron* **2010**, *66*, 5637.
42. Contelles, J. M.; Leon, R.; Morales, E.; Villarroy, M.; Garcia, A. G. *Tetrahedron Lett.* **2004**, *45*, 5203.
43. Bell, I. M.; Gallicchio, S. N.; Zartman, C. B.; Theberge, C. R.; Zhang, X. F. WO 2007/061694 A2 PCT Int. Appl., 2007.
44. (a) Hemmerling, H.-J.; Reiss, G. *Synthesis* **2009**, *6*, 985; (b) Wang, G.-W.; Miao, C.-B. *Green Chem.* **2006**, *8*, 1080; (c) Chanda; Kaushik; Dutta; Chandra, M.; Vishwakarma, J. N. *Indian J. Chem.* **2004**, *43B*, 2475.
45. Shestopalov, N. D.; Shestopalov, A.; Lyudmila, A.; Rodinovskaya. *Synthesis* **2008**, *1*, 1.
46. (a) Gudriniece, E.; Rigerte, B. SU 521260, 1976; *Chem. Abstr.* **1976**, *85*, 177041; (b) Rigerte, B.; Gudriniece, E. *Latv. PSR Zinat. Akad. Vestis. Kim. Ser.* **1977**, 601; *Chem. Abstr.* **1978**, *88*, 50345.