Tetrahedron 66 (2010) 4043–4048

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Solvent-free cascade reaction: direct multicomponent assembling of 2-amino-4*H*-chromene scaffold from salicylaldehyde, malononitrile or cyanoacetate and nitroalkanes

Michail N. Elinson *, Alexey I. Ilovaisky, Valentina M. Merkulova, Pavel A. Belyakov, Alexander O. Chizhov, Gennady I. Nikishin

N. D. Zelinsky Institute of Organic Chemistry, Leninsky prospect 47, 119991 Moscow, Russia

ARTICLE INFO

Article history:
Received 26 November 2009
Received in revised form 16 March 2010
Accepted 6 April 2010
Available online 10 April 2010

Keywords:
Solvent-free reactions
Salicylaldehyde
Malononitrile
Cyanoacetate
Nitroalkanes
2-Amino-4*H*-chromenes

ABSTRACT

The new type of solvent-free cascade reaction was found: the direct heating of the mixture of salicylaldehyde, malononitrile or cyanoacetate and nitroalkanes at 60 °C in the presence of catalytic amounts of KF or NaOAc results in the formation of 2-amino-4-(1-nitroalkyl)-4*H*-chromene-3-carbonitriles or methyl 2-amino-4-(1-nitroalkyl)-4*H*-chromene-3-carboxylates in 80–90% yields. Thus, the new simple and efficient solvent-free `one-pot' way to substituted medicinally privileged 2-amino-4*H*-chromene scaffold was found directly from such simple and reasonable starting compounds as salicylaldehyde, malononitrile or cyanoacetate and nitroalkanes.

1. Introduction

The discovery of new synthetic methodologies to facilitate the preparation of organic compounds is a pivotal focal point of research activity in the field of modern organic, bioorganic and medicinal chemistry.[1] One approach to address this challenge involves the development of multicomponent reactions (MCRs), in which three or more reactants are combined together in a single reaction flask to generate a product incorporating most of the atoms contained in the starting materials.[2]

In recent years the concept of `privileged medicinal structures or scaffolds'[3] has emerged as one of the guiding principles of drug discovery process. It involves the utilization of molecular frameworks with inherent potential for biological activity. These privileged scaffolds commonly consist of rigid hetero ring system that assigns well-defined orientation of appended functionalities for target recognition.[4]

The chromene moiety often appears as an important structural component in both biologically active and natural compounds. It is widely performed in natural alkaloids, flavonoids, tocopherols and anthocyanins.[5] Moreover, in recent years functionalized chromenes have played ever increasing role in the synthetic approaches to promising compounds in the field of medicinal chemistry.[6] Among different types of chromene systems, 2-amino-4*H*-chromenes (or 2-amino-4*H*-benzo[*b*]pyranes) are of particular utility as they belong to privileged medicinal scaffolds serving for generation of small-molecule ligands with highly pronounced spasmolitic-, diuretic-, anticoagulant- and antianaphylactic activities.[3a,3c,7] The current interest in 2-amino-4*H*-chromene derivatives arises from their potential application in the treatment of human inflammatory TNFα-mediated diseases, such as rheumatoid and psoriatic arthritis and in cancer therapy.[8]

Recently we suggested an electrocatalytic process as facile and convenient way to create diversely substituted medicinally privileged 2-amino-4*H*-chromene scaffold directly from salicylaldehydes and two different C–H acids.[9] The developed electrocatalytic system afforded the distinction between two C–H acids according to their reactivity and for the first time offered an efficient approach to the design and actual synthesis of privileged 2-amino-4*H*-chromene scaffold with a predefined arrangement of desired substituents. The electrocatalytic multicomponent reaction smoothly proceeded with salicylaldehydes bearing both electron-donating and electron-withdrawing groups, and allows for the selective and combined one-step introduction of the wide range of medicinally promising functionalities into privileged 2-amino-4*H*-chromene framework. Thus, fifteen previously inaccessible close structural

* Corresponding author. Tel.: +7 499 137 38 42; fax: +7 499 135 53 28; e-mail address: elinson@ioc.ac.ru (M.N. Elinson).

0040-4020/$ – see front matter © 2010 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2010.04.024

analogues of tumour antagonists HA14-1 and MX58151 have been synthesized. The electrocatalytic process was found to be advantageous in terms of selectivity and yields compare to classic chemical base catalysis.

But in the case of the nitroalkanes as one of C–H acids used in the electrocatalytic process the yields of the corresponding substituted 2-amino-4*H*-chromenes were only in the range of 65–70%, which could be connected with the undesired reduction of the nitro group at cathode.

Recently the progress in the field of solvent-free reactions have provided organic chemists with a new simple efficient synthetic method of great promise. This is connected with high efficiency and operational simplicity of the solvent-free processes.[10] The development of solvent-free organic synthesis methods has become an important research area. This is not only due to the need for the more efficient and less labour-intense methodologies for the synthesis of organic compounds, but also consequence of the increasing importance of the environmental considerations in chemistry. The elimination of volatile organic solvents in organic synthesis is also a most important goal in green chemistry.

Thus, solvent-free reactions have significant economical and ecological benefits when one performs several synthetic steps in one operation without isolating the reaction intermediates. The implication of the solvent-free process in base-activated multicomponent reactions (MCR) is highly promising as it allows for the combination of the synthetic virtues of the conventional MCR strategy with the ecological benefits and convenience of the solvent-free procedure. Thus, we were prompted to use a convenient and facile solvent-free MCR methodology for the synthesis of 2-amino-4*H*-chromene scaffold from salicylaldehydes, cyanoacetate or malononitrile and nitroalkanes.

2. Results and discussion

In the present study we report our results on the solvent-free direct `one-pot' cascade transformation of salicylaldehyde **1**, cyanoacetate or malononitrile **2a**,**b** and nitroalkanes **3a**–**j** into the substituted 2-amino-4-(1-nitroalkyl)-4*H*-chromenes **4a**–**o**. (Scheme 1).

First, to evaluate the synthetic potential of the procedure proposed and to optimize the general conditions, the solvent-free base initiated cascade transformation of salicylaldehyde **1**, methyl cyanoacetate **2a** and nitromethane **3a** into 2-amino-4*H*-chromene **4a** was studied (Table 1).

Table 1
Solvent-free cascade transformation of salicylaldehyde **1**, methyl cyanoacetate **2a** and nitromethane **3a** into 2-amino-4*H*-chromene **4a**[a]

Entry	Base	Base (mmol)	*t* (h)	Yield of **4a**[b] (%)
1	NaOAc	1	3	75
2	NaOAc	3	3	83
3	NaOAc	5	3	91
4	NaOAc	5	2	65[c,d]
5	NaOAc	5	1	39[c,e]
7	KF	1	1	78
8	KF	3	1	93

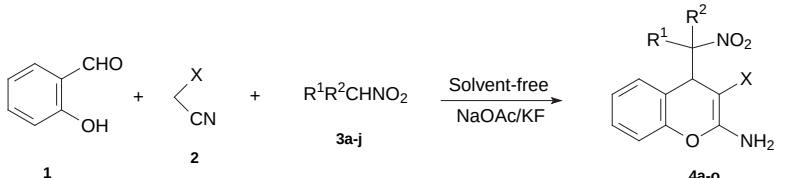
[a] 10 mmol of salicylaldehyde **1**, 10 mmol of methyl cyanoacetate **2a**, 10 mmol of nitromethane **3a**, 60 °C.
[b] Isolated yield.
[c] ^{1}H NMR data yields.
[d] Conversion of **1**—93%, 2-amino-4-(1-cyano-2-methoxy-2-oxoethyl)-4*H*-chromene-3-carboxylate **5a** was also found in the reaction mixture in 16% yield.
[e] Conversion of **1**—74%, 2-amino-4-(1-cyano-2-methoxy-2-oxoethyl)-4*H*-chromene-3-carboxylate **5a** was also found in the reaction mixture in 29% yield.

The best 91–93% yield of 2-amino-4*H*-chromene **4a** was achieved when the reaction was carried in the presence of 5 mmol of NaOAc (3 h at 60 °C) or 3 mmol of KF (1 h at 60 °C); entries 3 and 8 (Table 1).

Under the optimal conditions thus found, i.e., 5 mmol of NaOAc (3 h at 60 °C) or 3 mmoles of KF (1 h at 60 °C), salicylaldehyde **1**, C–H acids **2a**,**b** and nitrocompounds **3a**–**j** were transformed into corresponding substituted 2-amino-4*H*-chromenes **4a**–**o** in 80–93% yields (Table 2).

2-Amino-4*H*-chromenes **4b**,**f**–**j**,**l**–**o** were isolated as mixtures of diastereomers, the ratio was established by NMR data and is given in Table 2. For the compounds **4g** and **4f** NMR HSQCED and HMBC spectra were recorded to establish the position of all *C*-atoms. The comparison of experimental and calculated[11] NMR ^{13}C spectra indicated a (*R**, *R**) configuration for the main isomer of **4g** and (*R**, *S**) for the main isomer of **4f**.

In order to examine the mechanism of the new solvent-free multicomponent reaction, some other solvent-free reactions were carried out. The solvent-free reaction of salicylaldehyde **1** (10 mmol) with 2 equiv of nitromethane **3a** (20 mmol) in the presence of NaOAc (5 mmol) at 60 °C during 3 h resulted only in 2-(1-hydroxy-2-nitroethyl)phenol (Henry reaction adduct, NMR-data) formation in 8% yield (conversion of salicylaldehyde was 9%). Thus, nitromethane practically did not react with salicylaldehyde under these conditions. Analogous reactions of salicylaldehyde **1** (10 mmol) with 2 equiv of methyl cyanoacetate **2**a (20 mmol) led to



1

2

a X = CO_2CH_3
b X = CN

3a-j

a $R^1 = R^2 = H$
b $R^1 = CH_3$, $R^2 = H$
c $R^1 = C_2H_5$, $R^2 = H$
d $R^1 = R^2 = CH_3$
e $R^1 + R^2 = -(CH_2)_5-$
f $R^1 = Ph$, $R^2 = H$
g $R^1 = CH_2CH_2COCH_3$, $R^2 = H$
h $R^1 = CH_2CH_2COCH_3$, $R^2 = CH_3$
i $R^1 = CO_2CH_3$, $R^2 = H$
j $R^1 = CH_2CH_2CO_2CH_3$, $R^2 = CH_3$

4a-o

a $R^1 = R^2 = H$, X = CO_2CH_3
b $R^1 = CH_3$, $R^2 = H$, X = CO_2CH_3
c $R^1 = C_2H_5$, $R^2 = H$, X = CO_2CH_3
d $R^1 = R^2 = CH_3$, X = CO_2CH_3
e $R^1 + R^2 = -(CH_2)_5-$, X = CO_2CH_3
f $R^1 = Ph$, $R^2 = H$, X = CO_2CH_3
g $R^1 = CH_2CH_2COCH_3$, $R^2 = H$, X = CO_2CH_3
h $R^1 = CH_2CH_2COCH_3$, $R^2 = CH_3$, X = CO_2CH_3
i $R^1 = CO_2CH_3$, $R^2 = H$, X = CO_2CH_3
j $R^1 = CH_2CH_2CO_2CH_3$, $R^2 = CH_3$, X = CO_2CH_3
k $R^1 = R^2 = H$, X = CN
l $R^1 = C_2H_5$, $R^2 = H$, X = CN
m $R^1 = CH_2CH_2COCH_3$, $R^2 = H$, X = CN
n $R^1 = CH_2CH_2COCH_3$, $R^2 = CH_3$, X = CN
o $R^1 = CH_2CH_2CO_2CH_3$, $R^2 = CH_3$, X = CN

Scheme 1.

Table 2
Solvent-free multicomponent transformation of salicylaldehyde **1**, C–H acids **2a**, **b** and nitro- compounds **3a–j** into 2-amino-4*H*-chromenes **4a–o**[a]

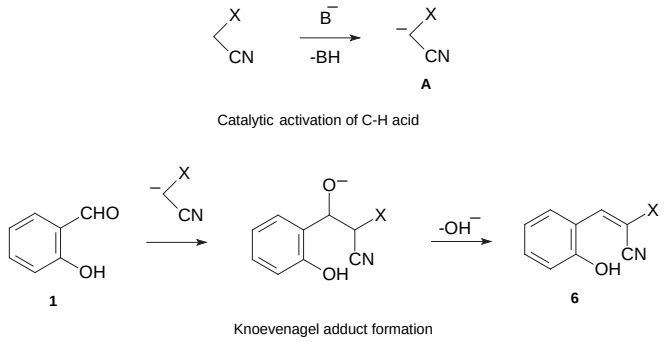
Entry	C–H acid	Nitro-compound	Base	Base (mmol)	*t* (h)	2-amino-4*H*-chromene, yield (%)[b]	Ratio of diastereomers[c]
1	**2a**	**3a**	KF	3	1	**4a**, 93	—
2	**2a**	**3b**	NaOAc	5	3	**4b**, 90	1:1
3	**2a**	**3c**	NaOAc	5	3	**4c**, 87	—
4	**2a**	**3d**	NaOAc	5	3	**4d**, 83	—
5	**2a**	**3d**	KF	3	1	**4d**, 85	—
6	**2a**	**3e**	KF	3	1	**4e**, 81	—
7	**2a**	**3f**	KF	3	1	**4f**, 89	1.6:1
8	**2a**	**3g**	KF	3	1	**4g**, 85	4.5:1
9	**2a**	**3h**	KF	3	1	**4h**, 82	30:1
10	**2a**	**3i**	KF	3	1	**4i**, 80	1:1
11	**2a**	**3j**	KF	3	1	**4j**, 85	12:1
12	**2b**	**3a**	NaOAc	5	3	**4k**, 82	—
13	**2b**	**3c**	KF	3	1	**4l**, 81	1:1
14	**2b**	**3g**	KF	3	1	**4m**, 83	1:1
15	**2b**	**3h**	NaOAc	5	3	**4n**, 79	1:1
16	**2b**	**3h**	KF	3	1	**4n**, 82	1:1
17	**2b**	**3j**	NaOAc	5	3	**4o**, 80	1.2:1
18	**2b**	**3j**	KF	3	1	**4o**, 83	1.2:1

[a] 10 mmol of salicylaldehyde **1**, 10 mmol of C–H acid **2**, 10 mmol of nitro-compound **3**, 60 °C.
[b] Isolated yield.
[c] ^{1}H NMR data.

methyl 2-amino-4-(1-cyano-2-methoxy-2-oxoethyl)-4*H*-chromene-3-carboxylate **5a** in 88% yield.

The solvent-free reaction of salicylaldehyde **1** (10 mmol), nitromethane **3a** (10 mmol) and methyl 2-amino-4-(1-cyano-2-methoxy-2-oxoethyl)-4*H*-chromene-3-carboxylate **5a** (10 mmol) in the presence of NaOAc (5 mmol) at 60 °C during 3 h resulted in methyl 2-amino-4-(nitromethyl)-4*H*-chromene-3-carboxylate **4a** formation in 88% yield and the solvent-free reaction of salicylaldehyde **1** (10 mmol), nitromethane **3a** (10 mmol) and (2-amino-3-cyano-4*H*-chromen-4-yl)malononitrile **5b** (10 mmol) in the presence of NaOAc (5 mmol) at 60 °C during 3 h resulted in 2-amino-4-(nitromethyl)-4*H*-chromene-3-carbonitrile **4k** formation in 85% yield.

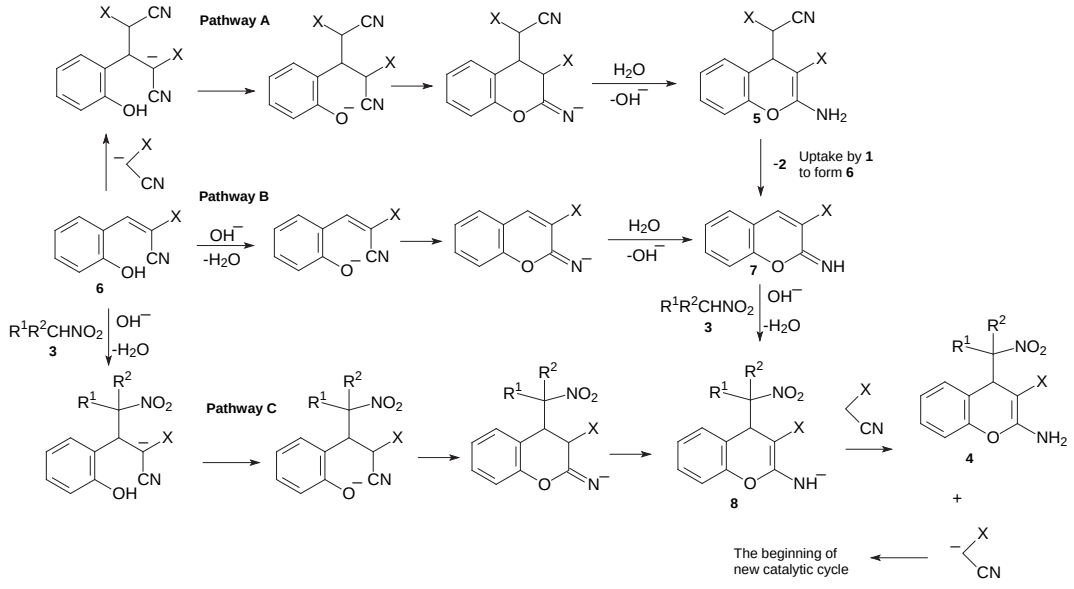
Taking into consideration all obtained data, the following reaction scheme was proposed for the direct solvent-free cascade transformation of salicylaldehyde **1**, cyanoacetate or malononitrile **2a**,**b** and nitroalkanes **3a–j** into the substituted 2-amino-4*H*-chromenes **4a–o** (Scheme 2). The initiation step of the catalytic cycle begins with the deprotonation of a molecule of the more active C–H acid by the action of catalyst, which leads to the formation of an anion **A**, which then reacts with salicylaldehyde **1** with the elimination of hydroxide anion and the formation of the Knoevenagel adduct **6** (Scheme 2).[12]



Scheme 2.

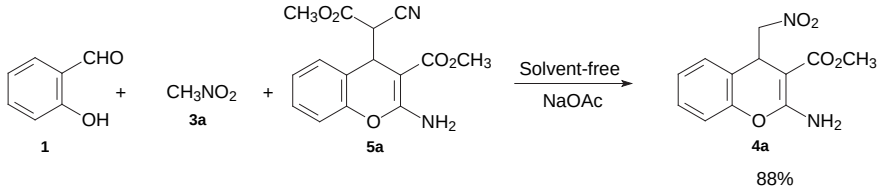
Next, three reaction pathways are possible for Knoevenagel adduct **6** (Scheme 3).

The Michael addition of anion of C–H acid **2** to the Knoevenagel adduct **6** followed by intramolecular cyclization leads to corresponding 2-amino-4*H*-chromene **5** (pathway A). 2-Amino-4*H*-chromene (**5a** X=COOMe) was detected in the reaction mixtures obtained when the solvent-free reaction of salicylaldehyde **1**, methyl cyanoacetate **2a** and nitromethane **3a** in the presence of NaOAc was accomplished in more short time (2 and 1 h instead of 3 h) in 16 and 29% yield based on starting salicylaldehyde **1** (Table 1, entries 4 and 5). Recently, O'Callaghan et al. have noted that in alcoholic solution (2-amino-3-cyano-4*H*-chromen-4-yl)malononitrile (**5b**, X=CN) could exist in equilibrium with corresponding 2-imino-2*H*-chromene-3-carbonitrile (**7b**, X=CN) and malononitrile (**2b**) under certain reaction conditions.[13] If such equilibrium exists in our case, the uptake of stronger C–H acid **2** from the



Scheme 3.

equilibrium by salicylaldehyde **1** could facilitate the base-promoted addition of weaker C–H acid **3** (nitroalkane) to 2-imino-2*H*-chromene **7**, what results in the full conversion of **5** into desired 2-amino-4*H*-chromene **4** during the solvent-free cascade process. This suggestion was especially confirmed by above mentioned solvent-free reaction of salicylaldehyde **1** (10 mmol), nitromethane **3a** (10 mmol) and methyl 2-amino-4-(1-cyano-2-methoxy-2-oxoethyl)-4*H*-chromene-3-carboxylate **5a** (10 mmol) in the presence of NaOAc (5 mmol) (60 °C, 3 h), which resulted in methyl 2-amino-4-(nitromethyl)-4*H*-chromene-3-carboxylate **4a** formation in 88% isolated yield (Scheme 4).



Scheme 4.

Thus, the solvent-free catalytic cascade transformation found offers a facile exchange of the substituent at 4-position of corresponding 4*H*-chromene cycle for another nucleophilic fragment under mild reaction conditions—a promising synthetic opportunity in the design of functionalized 2-amino-4*H*-chromene scaffold.

As for the pathway B (Scheme 3), it includes the hydroxide-promoted intramolecular cyclization of Knoevenagel adduct **6** into reactive 2-imino-2*H*-chromene **7**[13] with a subsequent base-promoted Michael addition of weaker C–H acid **3**. The following protonation of the combined adduct **8** by a molecule of C–H acid leads to the formation of 2-amino-4*H*-chromene **4** with the regeneration of anion of C–H acid **2**, which thus continues the catalytic cycle. The contribution of pathway C into the overall mechanistic scheme seems to be less probable, as it initially includes the addition of the anion of the weaker C–H acid **3** to **6** in the presence of stronger C–H acid **2**. Nevertheless, the pathway C could not be excluded from the overall scheme of the solvent-free catalytic cascade process (Scheme 3).

3. Conclusion

In conclusion, the new simple solvent-free catalytic cascade process can produce, under mild conditions, an effective multicomponent transformation of salicylaldehydes, nitroalkanes and malononitrile or cyanoacetate into 4-nitroalkyl substituted 2-amino-4*H*-chromenes in high 80–90% yields. This novel solvent-free catalytic cascade process offers a facile and convenient way to create substituted medicinally privileged 2-amino-4*H*-chromene scaffold—the approved basis for the generation of small-molecule ligands with different biomedical properties including highly pronounced anticancer activities. Compared to known MCR protocols, the solvent-free catalytic cascade procedure represents the most efficient approach to the 4-nitroalkyl substituted 2-amino-4*H*-chromene scaffold. The reversibility of 2-amino-4*H*-chromenes **5** formation revealed during mechanistic investigations seems to be an important feature of the solvent-free catalytic cascade process, that is, promising for the synthesis of novel types of functionalized 2-amino-4*H*-chromenes by the exchange of the corresponding C–H acid residue in 4-position of 4*H*-chromene cycle for another nucleophilic species. The developed solvent-free multicomponent procedure utilizes simple equipment and requires reasonable starting materials. It is easily carried out, the reaction products were isolated by easy work-up procedure and do not need any further purification steps. Therefore, this novel type of MCR brings us a step closer to the notion of `ideal synthesis'.[14]

4. Experimental section

4.1. General remarks

All melting points were measured with a Gallenkamp melting point apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded with a Bruker Avance II-300 and Bruker Avance II-600 spectrometers at ambient temperature. HSQCED and HMBC spectra were recorded with Bruker Avance II-600 instrument. Chemical shifts values are relative to Me_4Si. IR spectra were registered with a SPECORD M82 spectrometer in KBr pellets. Mass-spectra (EI=70 eV) were obtained directly with a Finningan MAT INCOS 50 spectrometer. The ES mass spectra were recorded with a Finnigan MAT LCQ instrument. Spray capillary voltage 4530 V. A methanolic solution of the sample was injected by syringe at 10 μL/min; MS spectra were measured at positive mode (registration range from *m*/*z* 100 to *m*/*z* 2000). Interface capillary temperature was 220 °C, sheath gas flow (nitrogen) 19.4 a.u., auxiliary gas flow 0.4 a.u. Activation time was 30 ms. Activation energy was 30% from relative max. collision energy. Nitrocompounds **3f**[15], **3g**[16], **3h**[17], **3j**[18], 2-amino-4-(1-cyano-2-methoxy-2-oxoethyl)-4*H*-chromene-3-carboxylate **5a** and (2-amino-3-cyano-4*H*-chromen-4-yl)malononitrile **5b**[19] were synthesized by known methods. All other chemicals were purchased from commercial sources.

4.2. Typical procedure

4.2.1. Synthesis of methyl 2-amino-4H-chromene-3-carboxylates. A mixture of salicylaldehyde (1.22 g, 10 mmol), methyl cyanoacetate (0.99 g, 10 mmol), nitromethane (0.61 g, 10 mmol) and sodium acetate (0.41 g, 5 mmol) was stirred for 3 h at 60 °C. Afterwards, the reaction mixture was cooled, diluted with water (50 ml) and extracted with chloroform (2×20 mL). The organic phase was washed with water (2×20 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The residue obtained was triturated with ether (2 mL) and filtered to isolate the solid product, which was then twice washed with ether (2 mL), and dried under reduced pressure.

4.2.2. Synthesis of methyl 2-amino-4H-chromene-3-carbonitriles. The procedure was the same as given above, except after the reaction mixture was diluted with water (50 mL), the solid was filtered and washed with water (2×20 mL), ether (2×5 mL) and dried under reduced pressure.

*4.2.3. Methyl 2-amino-4-(nitromethyl)-4H-chromene-3-carboxylate (**4a**).* White solid. Yield 2.45 g (93%); mp 108–110 °C (lit. mp[9] 108–110 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.79 (s, 3H, OCH_3), 4.38 (dd, $^2J_{H,H}$=11.2 Hz, $^3J_{H,H}$=7.9 Hz, 1H), 4.54 (dd, $^2J_{H,H}$=11.2 Hz, $^3J_{H,}$

$_H$=4.6 Hz, 1H), 4.63 (dd, $^3J_{H,H}$=7.9 Hz, $^3J_{H,H}$=4.6 Hz, 1H), 6.50 (br s, 2H, NH_2), 7.02 (d, $^3J_{H,H}$=8.5 Hz, 1H, Ar), 7.07–7.28 (m, 3H, Ar) ppm.

*4.2.4. Methyl 2-amino-4-(1-nitroethyl)-4H-chromene-3-carboxylate (**4b**).* Viscous yellow oil. Yield 2.50 g (90%); diastereomeric ratio 1:1; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.18 (d, $^3J_{H,H}$=6.6 Hz, 1.5H, CH_3), 1.37 (d, $^3J_{H,H}$=5.9 Hz, 1.5H, CH_3), 3.70 (s, 1.5H, CH_3), 3.82 (s, 1.5H, CH_3), 4.49–4.60 (m, 1H), 4.69–4.81 (m, 1H), 6.1–6.9 (br s, 2H, NH_2), 6.93–7.32 (m, 4H, Ar) ppm; ^{13}C NMR (75 MHz, $CDCl_3$, 24 signals for 13 carbons) δ 11.7, 14.3, 39.5 (2C), 50.8, 51.3, 72.1, 73.6, 85.8, 88.1, 115.8, 116.2, 119.6, 122.2, 124.9 (2C), 128.4, 128.5, 128.7, 128.9, 150.5, 150.6, 162.5, 162.6, 168.7, 169.1 ppm; IR (KBr): ν=3456, 3316, 2992, 2952, 1684, 1628, 1548, 1488, 1440, 1300 cm^{-1}; MS (EI): *m*/*z* (%)= 278 (1) $[M]^+$, 232 (8), 204 (91), 172 (100), 145 (78), 143 (62), 116 (55), 89 (95), 63 (80), 39 (75). Anal. Calcd (%) for $C_{13}H_{14}N_2O_5$: C, 56.11; H, 5.07; N, 10.07. Found (%): C, 55.85; H, 4.89; N, 9.85.

*4.2.5. Methyl 2-amino-4-(1-nitropropyl)-4H-chromene-3-carboxylate (**4c**).* White solid. Yield 2.54 g (87%); mp 138 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.86 (t, $^3J_{H,H}$=7.3 Hz, 3H, CH_3), 1.53–1.69 (m, 1H), 1.95–2.14 (m, 1H), 3.73 (s, 3H, CH_3), 4.27–4.38 (m, 1H), 4.47 (d, $^3J_{H,H}$=6.2 Hz, 1H), 6.0–6.9 (br s, 2H, NH_2), 7.03 (d, $^3J_{H,H}$=8.1 Hz, 1H, Ar), 7.09–7.21 (m, 2H, Ar), 7.23–7.31 (m, 1H, Ar) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 10.5, 22.7, 38.9, 50.9, 73.2, 95.5, 116.2, 122.4, 124.8, 128.3, 128.6, 150.7, 162.6, 169.0 ppm; IR (KBr): ν=3456, 3316, 2952, 1684, 1640, 1544, 1488, 1440, 1228 cm^{-1}; MS (EI): *m*/*z* (%)= 204 (100) $[M-EtCHNO_2]^+$, 172 (40), 145 (5), 116 (6), 89 (7), 63 (4), 39 (13). Anal. Calcd (%) for $C_{14}H_{16}N_2O_5$: C, 57.53; H, 5.52; N, 9.58. Found (%): C, 57.39; H, 5.48; N, 9.42.

*4.2.6. Methyl 2-amino-4-(1-methyl-1-nitroethyl)-4H-chromene-3-carboxylate (**4d**).* Yellow solid. Yield 2.48 g (85%); mp 133 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.27 (s, 3H, CH_3), 1.51 (s, 3H, CH_3), 3.75 (s, 3H, CH_3), 4.69 (s, 1H), 5.9–6.9 (br s, 2H, NH_2), 6.99–7.12 (m, 3H, Ar), 7.21–7.30 (m, 1H, Ar) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.1, 24.2, 43.1, 50.8, 73.5, 94.1, 115.7, 122.0, 124.8, 128.5, 128.6, 151.0, 163.1, 169.3 ppm; IR (KBr): ν=3432, 3324, 2996, 2944, 1684, 1636, 1536, 1484, 1440, 1348 cm^{-1}; MS (EI): *m*/*z* (%)=246 (2) $[M-NO_2]^+$, 204 (100), 172 (55), 145 (16), 116 (9), 89 (16), 63 (8), 39 (42). Anal. Calcd (%) for $C_{14}H_{16}N_2O_5$: C, 57.53; H, 5.52; N, 9.58. Found (%): C, 57.37; H, 5.39; N, 9.44.

*4.2.7. Methyl 2-amino-4-(1-nitrocyclohexyl)-4H-chromene-3-carboxylate (**4e**).* White solid. Yield 2.69 g (81%); mp 152 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.99–1.46 (m, 5H), 1.50–1.68 (m, 3H), 2.08 (d, *J*=13.0 Hz, 1H), 2.58 (d, *J*=13.0 Hz, 1H), 3.74 (s, 3H, CH_3), 4.42 (s, 1H), 6.0–6.9 (br s, 2H, NH_2), 6.99–7.14 (m, 3H, Ar), 7.22–7.31 (m, 1H, Ar) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.8, 22.1, 24.3, 28.4, 31.5, 44.6, 50.8, 73.6, 98.0, 115.7, 121.8, 124.5, 128.4, 129.0, 151.2, 163.3, 169.4 ppm; IR (KBr): ν=3372, 3284, 2932, 2852, 1680, 1628, 1540, 1484, 1444, 1300 cm^{-1}; MS (ES): *m*/*z*=355 $[M+Na]^+$, 333 $[M+H]^+$, 226, 204. Anal. Calcd (%) for $C_{17}H_{20}N_2O_5$: C, 61.44; H, 6.07; N, 8.43. Found (%): C, 61.27; H, 6.35; N, 8.32.

*4.2.8. Methyl 2-amino-4-[nitro(phenyl)methyl]-4H-chromene-3-carboxylate (**4f**).* White solid. Yield 3.03 g (89%); diastereomeric ratio (*R**,*S**)-**4f** : (*R**,*R**)-**4f**=1.6:1; mp 112–118 °C; (*R**,*S**)–**4f**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.33 (s, 3H, CH_3), 4.86 (d, *J*=8.8 Hz, 1H), 5.32 (d, *J*=8.8 Hz, 1H), 6.0–6.9 (br s, 2H, NH_2), 6.77–6.91 (m, 1H, Ar), 6.99–7.47 (m, 8H, Ar) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 40.1, 50.3, 72.9, 95.8, 116.0, 122.6, 124.7, 127.7, 127.9 (2C), 128.5 (2C), 129.2, 129.3, 131.7, 150.8, 162.6, 168.5 ppm; (*R**,*R**)-**4f**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.82 (s, 3H, CH_3), 5.08 (d, *J*=4.8 Hz, 1H), 5.55 (d, *J*=4.8 Hz, 1H) 6.0–6.9 (br s, 2H, NH_2), 6.77–6.91 (m, 1H, Ar), 6.99–7.47 (m, 8H, Ar) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 40.2, 51.1, 73.2, 93.7, 115.6, 120.5, 124.4, 128.5 (2C), 128.6 (2C), 128.8, 129.1, 129.2, 131.1, 150.9, 162.6, 168.6 ppm; IR (KBr): ν=3400, 3288, 2896, 1672, 1624, 1552, 1528, 1484, 1448 cm^{-1}; MS (EI): *m*/*z* (%)=294 (0.5) $[M-NO_2]^+$, 262 (4), 204 (100), 172 (55), 145 (34), 143 (28), 116 (12), 91 (62), 63 (15), 39 (13). Anal. Calcd (%) for $C_{18}H_{16}N_2O_5$: C, 63.52; H, 4.74; N, 8.23. Found (%): C, 63.42; H, 4.53; N, 8.17.

*4.2.9. Methyl 2-amino-4-(1-nitro-4-oxopentyl)-4H-chromene-3-carboxylate (**4g**).* White solid. Yield 2.84 g (85%); diastereomeric ratio (*R**,*R**)-**4g** : (*R**,*S**)-**4g**=4.5:1; mp 131–132 °C; (*R**,*R**)-**4g**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.85–2.0 (m, 1H), 2.06 (s, 3H, CH_3), 2.11–2.52 (m, 3H), 3.72 (s, 3H, CH_3), 4.42–4.54 (m, 2H), 6.1–6.9 (br s, 2H, NH_2), 6.94–7.32 (m, 4H, Ar) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.1, 29.8, 39.1, 39.2, 50.8, 72.6, 92.5, 116.2, 121.9, 124.8, 128.4, 128.7, 150.6, 162.6, 168.8, 206.2 ppm; (*R**,*S**)-**4g**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.65–1.75 (m, 1H), 2.06 (s, 3H, CH_3), 2.11–2.52 (m, 3H), 3.81 (s, 3H, CH_3), 4.61–4.68 (m, 2H) 6.1–6.9 (br s, 2H, NH_2), 6.94–7.32 (m, 4H, Ar) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.6, 29.7, 39.5, 39.8, 51.3, 73.5, 90.8, 115.9, 119.8, 124.7, 128.6, 128.9, 150.5, 162.5, 168.6, 206.5 ppm; IR (KBr): ν=3392, 3288, 2952, 1688, 1708, 1628, 1548, 1488, 1440, 1296 cm^{-1}; MS (EI): *m*/*z* (%)=288 (0.5) $[M-NO_2]^+$, 230 (2), 204 (100), 172 (66), 145 (22), 143 (15), 116 (9), 89 (12), 63 (7), 43 (91). Anal. Calcd (%) for $C_{16}H_{18}N_2O_6$: C, 57.48; H, 5.43; N, 8.38. Found (%): C, 57.22; H, 5.65; N, 8.12.

*4.2.10. Methyl 2-amino-4-(1-methyl-1-nitro-4-oxopentyl)-4H-chromene-3-carboxylate (**4h**).* White solid. Yield 2.85 g (82%); diastereomeric ratio 30:1; mp 160–162 °C; major diastereomer: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.19 (s, 3H, CH_3), 1.76–1.94 (m, 1H), 2.11 (s, 3H, CH_3), 2.12–2.42 (m, 2H), 2.55–2.72 (m, 1H), 3.79 (s, 3H, CH_3), 4.72 (s, 1H), 6.0–6.9 (br s, 2H, NH_2), 6.93–7.17 (m, 3H, Ar), 7.20–7.33 (m, 1H, Ar) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.0, 29.9, 30.3, 38.0, 44.0, 50.9, 73.4, 97.4, 115.8, 121.8, 125.0, 128.5, 128.6, 151.2, 163.3, 169.3, 206.2 ppm; minor diastereomer: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.37 (s, 3H, CH_3), 2.10 (s, 3H, CH_3), 3.70 (s, 3H, CH_3), 4.57 (s, 1H) (all other signals are hidden by the signals of the major diastereomer); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.7, 27.6, 38.1, 45.0, 50.8, 96.1, 116.1, 124.6, 128.7, 129.3 ppm (all other signals are hidden by the signals of the major diastereomer); IR (KBr): ν=3432, 3312, 2952, 1712, 1688, 1604, 1544, 1484, 1440, 1300 cm^{-1}; MS (ES): *m*/*z*=371 $[M+Na]^+$, 349 $[M+H]^+$, 226, 204. Anal. Calcd (%) for $C_{17}H_{20}N_2O_6$: C, 58.61; H, 5.79; N, 8.04. Found (%): C, 58.47; H, 5.65; N, 8.12.

*4.2.11. Methyl 2-amino-4-(2-methoxy-1-nitro-2-oxoethyl)-4H-chromene-3-carboxylate (**4i**).* White solid. Yield 2.58 g (80%); diastereomeric ratio 1:1; mp 144–146 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.54 (s, 1.5H, CH_3), 3.78 (s, 3H, CH_3), 3.81 (s, 1.5H, CH_3), 4.93 (d, $^3J_{H,H}$=5.8 Hz, 0.5H), 5.00 (d, $^3J_{H,H}$=2.9 Hz, 0.5H), 5.31 (d, $^3J_{H,H}$=2.9 Hz, 0.5H), 5.40 (d, $^3J_{H,H}$=5.8 Hz, 0.5H), 6.1–6.9 (br s, 2H, NH_2), 6.98–7.41 (m, 4H, Ar) ppm; ^{13}C NMR (75 MHz, $CDCl_3$, 27 signals for 14 carbons) δ 36.8, 37.2, 51.2, 51.2, 52.9, 53.3, 71.7, 72.6, 91.2, 91.3, 115.8, 116.3, 119.4, 120.1, 124.8 (2C), 128.2, 129.0, 129.1, 129.2, 150.5, 150.9, 162.5, 162.8, 163.5, 163.9, 168.3, 168.4 ppm; IR (KBr): ν=3440, 3316, 2972, 1744, 1692, 1628, 1560, 1532, 1488, 1444 cm^{-1}; MS (EI): *m*/*z* (%)=204 (33), 172 (42), 145 (81), 143 (54), 89 (38), 73 (100), 63 (36), 42 (42). Anal. Calcd (%) for $C_{14}H_{14}N_2O_7$: C, 52.18; H, 4.38; N, 8.69. Found (%): C, 52.07; H, 4.30; N, 8.53.

*4.2.12. Methyl 2-amino-4-(4-methoxy-1-methyl-1-nitro-4-oxobutyl)--4H-chromene-3-carboxylate (**4j**).* White solid. Yield 3.09 g (85%); diastereomeric ratio 12:1; mp 134–136 °C; major diastereomer: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.22 (s, 3H, CH_3), 1.83–1.96 (m, 1H), 2.02–2.16 (m, 1H), 2.16–2.31 (m, 1H), 2.67–2.82 (m, 1H), 3.66 (s, 3H, CH_3), 3.79 (s, 3H, CH_3), 4.73 (s, 1H), 5.9–6.9 (br s, 2H, NH_2), 6.99–7.17 (m, 3H, Ar), 7.21–7.34 (m, 1H, Ar) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 15.8, 28.6, 31.4, 43.9, 50.8, 51.7, 73.2, 97.1, 115.8, 121.7, 124.9, 128.5, 128.6, 151.1, 163.3, 169.2, 172.4 ppm; minor diastereomer: ^{1}H NMR

(300 MHz, $CDCl_3$) δ 1.42 (s, 3H, CH_3), 3.64 (s, 3H, CH_3), 3.72 (s, 3H, CH_3), 4.59 (s, 1H) ppm (all other signals are hidden by the signals of the major diastereomer); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.6, 44.9, 95.9, 116.0, 124.6, 129.1 ppm (all other signals are hidden by the signals of the major diastereomer); IR (KBr): ν=3432, 3308, 3000, 2952, 1728, 1688, 1604, 1544, 1484, 1440 cm^{-1}; MS (ES): m/z=387 $[M+Na]^+$, 365 $[M+H]^+$, 226, 204. Anal. Calcd (%) for $C_{17}H_{20}N_2O_7$: C, 56.04; H, 5.53; N, 7.69. Found (%): C, 55.87; H, 5.45; N, 7.53.

*4.2.13. 2-Amino-4-(nitromethyl)-4H-chromene-3-carbonitrile (**4k**).* Yellowish solid. Yield 1.89 g (82%); mp 139–140 °C (lit.mp[9] 139–140 °C); ^1H NMR (300 MHz, DMSO-d_6) δ 4.31 (t, $^3J_{H,H}$=5.1 Hz, 1H), 4.66 (dd, $^2J_{H,H}$=12.5 Hz, $^3J_{H,H}$=5.1 Hz, 1H), 4.79 (dd, $^2J_{H,H}$=12.5 Hz, $^3J_{H,H}$=5.1 Hz, 1H), 7.03 (d, $^3J_{H,H}$=8.0 Hz, 1H, Ar), 7.17 (s, 2H, NH_2), 7.17 (t, $^3J_{H,H}$=8.0 Hz, 1H, Ar), 7.32 (t, $^3J_{H,H}$=8.0 Hz, 1H, Ar), 7.34 (d, $^3J_{H,H}$=8.0 Hz, 1H, Ar) ppm.

*4.2.14. 2-Amino-4-(1-nitropropyl)-4H-chromene-3-carbonitrile (**4l**).* Yellowish solid. Yield 2.10 g (81%), diastereomeric ratio 1:1; mp 189–190 °C; ^1H NMR (300 MHz, DMSO-d_6) δ 0.83 (t, J=7.3 Hz, 1.5H, CH_3), 0.85 (t, J=7.3 Hz, 1.5H, CH_3), 1.68–2.10 (m, 2H), 4.06 (d, J=6.6 Hz, 0.5H), 4.14 (d, J=4.8 Hz, 0.5H), 4.47–4.57 (m, 0.5H), 4.58–4.67 (m, 0.5H), 6.98–7.11 (m, 1H, Ar), 7.14–7.38 (m, 5H, Ar, NH_2) ppm; ^{13}C NMR (75 MHz, DMSO-d_6, 26 signals for 13 carbons) δ 10.2, 10.3, 23.1, 23.3, 39.7, 39.8, 48.9, 49.7, 94.6, 95.2, 116.2, 116.3, 120.1, 120.2, 120.4, 120.8, 124.8, 124.9, 128.6, 128.9, 129.2, 129.3, 149.9, 150.2, 163.3, 163.5 ppm; IR (KBr): ν=3436, 3332, 3212, 2976, 2204, 1648, 1608, 1540, 1492, 1416 cm^{-1}; MS (ES): m/z=282 $[M+Na]^+$, 193, 171. Anal. Calcd (%) for $C_{13}H_{13}N_3O_3$: C, 60.22; H, 5.05; N, 16.21. Found (%): C, 60.03; H, 4.95; N, 15.98.

*4.2.15. 2-Amino-4-(1-nitro-4-oxopentyl)-4H-chromene-3-carbonitrile (**4m**).* Yellowish solid. Yield 2.50 g (83%), diastereomeric ratio 1:1; mp 139–140 °C; ^1H NMR (300 MHz, DMSO-d_6) δ 2.02 (s, 1.5H, CH_3), 2.04 (s, 1.5H, CH_3), 2.40–2.57 (m, 4H), 4.14 (d, J=5.9 Hz, 0.5H), 4.20 (d, J=4.0 Hz, 0.5H), 4.55–4.62 (m, 0.5H), 4.62–4.72 (m, 0.5H), 7.01–7.10 (m, 1H, Ar), 7.13–7.39 (m, 5H, Ar, NH_2) ppm; ^{13}C NMR (75 MHz, DMSO-d_6, 28 signals for 15 carbons) δ 23.2, 23.4, 29.7 (2C), 38.5, 38.7, 39.9 (2C), 49.0, 49.4, 91.9, 92.4, 116.2, 116.3, 119.8, 119.9, 120.2, 120.5, 124.8, 124.9, 128.6, 128.7, 129.2, 129.3, 150.0, 150.1, 163.3, 163.4, 206.8, 206.9 ppm; IR (KBr): ν=3384, 3320, 3204, 2196, 1712, 1644, 1608, 1544, 1416 cm^{-1}; MS (ES): m/z=324 $[M+Na]^+$, 171. Anal. Calcd (%) for $C_{15}H_{15}N_3O_4$: C, 59.79; H, 5.02; N, 13.95. Found (%): C, 59.52; H, 4.95; N,13.74.

*4.2.16. 2-Amino-4-(1-methyl-1-nitro-4-oxopentyl)-4H-chromene-3-carbonitrile (**4n**).* Yellowish solid. Yield 2.58 g (82%); diastereomeric ratio 1:1; mp 141–143 °C; ^1H NMR (600 MHz, DMSO-d_6) δ 1.19 (s, 1.5H, CH_3), 1.31 (s, 1.5H, CH_3), 1.77–1.84 (m, 0.5H), 2.05–2.11 (m, 0.5H), 2.04 (s, 1.5H, CH_3), 2.06 (s, 1.5H, CH_3), 2.16–2.34 (m, 2H), 2.46–2.58 (m, 1H), 4.14 (s, 0.5H), 4.16 (s, 0.5H), 6.97–7.37 (m, 4H, Ar), 7.37 (s, 2H, NH_2) ppm; ^{13}C NMR (151 MHz, DMSO-d_6, 30 signals for 16 carbons) δ 16.5, 18.0, 28.3, 29.7, 29.8, 29.9, 37.07 (2C), 45.6, 45.7, 49.2, 49.3, 95.7, 96.6, 116.1, 116.2, 119.88 (2C), 120.3, 120.9, 124.3, 124.5, 128.3, 129.2, 129.3, 129.6, 150.6, 150.7, 164.1, 164.4, 206.4, 206.7 ppm; IR (KBr): ν=3456, 3328, 3208, 2192, 1712, 1652, 1600, 1575, 1540 cm^{-1}; MS (ES): m/z=338 $[M+Na]^+$, 171. Anal. Calcd (%) for $C_{16}H_{17}N_3O_4$: C, 60.94; H, 5.43; N, 13.33. Found (%): C, 60.72; H, 5.35; N, 13.15.

*4.2.17. Methyl 4-(2-amino-3-cyano-4H-chromen-4-yl)-4-nitropentanoate (**4o**).* Yellowish solid. Yield 2.75 g (83%); diastereomeric ratio 1.2:1; mp 121–123 °C; major diastereomer: ^1H NMR (600 MHz, DMSO-d_6) δ 1.24 (s, 3H, CH_3), 2.04–2.18 (m, 2H), 2.27–2.46 (m, 2H), 3.58 (s, 3H, OCH_3), 4.16 (s, 1H), 7.00–7.38 (m, 4H, Ar), 7.43 (s, 2H, NH_2) ppm; ^{13}C NMR (151 MHz, DMSO-d_6) δ 16.5, 28.2, 31.2, 45.6, 49.1, 51.7, 96.4, 116.2, 119.7, 120.8, 124.9, 128.4, 129.4, 150.7, 164.2, 172.2 ppm; minor diastereomer: ^1H NMR (600 MHz, DMSO-d_6) δ 1.35 (s, 3H, CH_3), 1.84–1.91 (m, 1H), 2.04–2.18 (m, 1H), 2.27–2.46 (m, 2H), 3.56 (s, 3H, OCH_3), 4.18 (s, 1H), 7.00–7.38 (m, 1H, Ar), 7.39 (s, 2H, NH_2) ppm; ^{13}C NMR (151 MHz, DMSO-d_6) δ 18.0, 28.1, 29.6, 45.7, 49.2, 51.6, 95.6, 116.2, 119.7, 120.3, 124.6, 128.4, 129.4, 150.7, 164.4, 172.3 ppm; IR (KBr): ν=3432, 3324, 3204, 2196, 1740, 1648, 1604, 1576, 1528 cm^{-1}; MS (ES): m/z=354 $[M+Na]^+$, 171. Anal. Calcd (%) for $C_{16}H_{17}N_3O_5$: C, 58.00; H, 5.17; N, 12.68. Found (%): C, 58.15; H, 5.37; N, 12.49.

Acknowledgements

The authors gratefully acknowledge the financial support of the Russian Foundation for Basic Research (Project No. 09-03-00003).

References and notes

1. (a) Thompson, L. A. *Curr. Opin. Chem. Biol.* **2000**, *4*, 324–337; (b) Nefzi, A.; Ostresh, J. M.; Houghten, R. A. *Chem. Rev.* **1997**, *97*, 449–472.
2. (a) Weber, L. *Drug Disc. Today* **2002**, *7*, 143–147; (b) Dömling, A. *Curr. Opin. Chem. Biol.* **2002**, *6*, 306–313.
3. The term `privileged scaffolds or structures' was originally introduced by Merck researchers in their work on benzodiazepins: Evans, B. E.; Rittle, K. E.; Bock, G.; DiPardo, R. M.; Freidinger, R. M.; Whitter, W. L.; Lundell, G. F.; Veber, D. F.; Anderson, P. S.; Chang, R. S. L.; Lotti, V. G.; Cerino, D. J.; Chen, T. B.; Kling, P. J.; Kunkel, K. A.; Springer, J. P.; Hirshfield, J. *J. Med. Chem.* **1988**, *31*, 2235–2246 for reviews see: (a) DeSimone, R. W.; Currie, K. S.; Mitchell, S. A.; Darrow, J. W.; Pippin, D. A. *Comb. Chem. High Throughput Screen.* **2004**, *7*, 473–493; (b) Triggle, D. J. *Cell. Mol. Neurobiol.* **2003**, *23*, 293–303; (c) Patchett, A. A.; Nargund, R. P. *Annu. Rep. Med. Chem.* **2000**, *35*, 289–298.
4. Poupaert, J.; Carato, P.; Colacino, E. *Curr. Med. Chem.* **2005**, *12*, 877–885.
5. For examples of natural compounds containing the chromene fragment, see: (a) *The Flavonoids—Advances in Research*; Harborne, J. B., Ed.; Chapman & Hall: London, UK, 1988; (b) Parmar, V. S.; Jain, S. C.; Bisht, K. S.; Jain, R.; Taneja, P.; Jha, A.; Tyagi, O. D.; Prasad, A. K.; Wengel, J.; Olsen, C. E.; Boll, P. M. *Phytochemistry* **1997**, *46*, 597–674; (c) Gill, M. *Aust. J. Chem.* **1995**, *48*, 1–26; (d) Bohm, B. A.; Choy, J. B.; Lee, A. Y.-M. *Phytochemistry* **1989**, *28*, 501–504; (e) Iacobucci, G. A.; Sweeny, J. G. *Tetrahedron* **1983**, *39*, 3005–3038.
6. For recent reports, see: (a) Sun, W.; Cama, L. J.; Birzin, E. T.; Warrier, S.; Locco, L.; Mosley, R.; Hammond, M. L.; Rohrer, S. P. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 1468–1472; (b) Stachulski, A. V.; Berry, N. G.; Low, A. C. L.; Moores, S.; Row, E.; Warhurst, D. C.; Adagu, I. S.; Rossignol, J.-F. *J. Med. Chem.* **2006**, *49*, 1450–1454; (c) Garino, C.; Bihel, F.; Pietrancosta, N.; Laras, Y.; QuÅlÅver, G.; Woo, I.; Klein, P.; Bain, J.; Boucher, J.-L.; Kraus, J.-L. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 135–138.
7. (a) Bonsignore, L.; Loy, G.; Secci, D.; Calignano, A. *Eur. J. Med. Chem.* **1993**, *28*, 517–520; (b) Foye, W. O. *Prinicipi di Chemico Farmaceutica*; Piccin: Padova, PD, 1991; p 416; (c) Witte, E.C.; Neubert, P.; Roesch, A. Ger. Offen. DE 3427985, 1986. *Chem. Abstr.* **1986**, *104*, 224915f; (d) Andreani, L. L.; Lapi, E. *Boll. Chim. Farm.* **1960**, *99*, 583–587.
8. (a) Skommer, J.; Wlodkowic, D.; Mättö, M.; Eray, M.; Pelkonen, J. *Leukemia Res.* **2006**, *30*, 322–331, and references therein; (b) Kemnitzer, W.; Kasibhatla, S.; Jiang, S.; Zhang, H.; Zhao, J.; Jia, S.; Xu, L.; Crogan-Grundy, C.; Denis, R.; Barriault, N.; Vaillancourt, L.; Charron, S.; Dodd, J.; Attardo, G.; Labrecque, D.; Lamothe, S.; Gourdeau, H.; Tseng, B.; Drewe, J.; Cai, S. X. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 4745–4751; (c) Gourdeau, H.; Leblond, L.; Hamelin, B.; Desputeau, C.; Dong, K.; Kianicka, I.; Custeau, D.; Bourdeau, C.; Geerts, L.; Cai, S. X.; Drewe, J.; Labrecque, D.; Kasibhatla, S.; Tseng, B. *Mol. Cancer Ther.* **2004**, *3*, 1375–1384.
9. Elinson, M. N.; Dorofeev, A. S.; Miloserdov, F. M.; Ilovaisky, A. I.; Feducovich, S. K.; Belyakov, P. A.; Nikishin, G. I. *Adv. Synth. Catal.* **2008**, *350*, 591–601.
10. Tanaka, K. *Solvent-free Organic Synthesis*; Wiley-VCH: Weinheim, 2003.
11. Ananikov, V. P. *Cent. Eur. J. Chem. (CEJC)* **2004**, *2*, 196–213.
12. Patai, S.; Israeli, Y. *J. Chem. Soc.* **1960**, 2025–2030.
13. ÓCallaghan, C. N.; McMurry, T. B.; ÓBrein, J. E. *J. Chem. Soc., Perkin Trans. 1* **1995**, *4*, 417–420.
14. 'Towards the ideal synthesis' Wender, P. A.; Handy, S. T.; Wright, D. L. *Chem. Ind.* **1997**, 765–769.
15. Kornblum, N.; Larson, H. O.; Blackwood, R. K.; Mooberry, D. D.; Oliveto, E. P.; Graham, G. E. *J. Am. Chem. Soc.* **1956**, *70*, 1497–1501.
16. Lewellyn, M. E.; Tarbell, D. S. *J. Org. Chem.* **1974**, *39*, 1407–1410.
17. Ballini, R.; Bosica, G. *Tetrahedron Lett.* **1996**, *37*, 8027–8030.
18. Ballini, R.; Bosica, G. *Eur. J. Org. Chem.* **1998**, 355–357.
19. Roudier, J. F.; Foucaud, A. *Synthesis* **1984**, 159–160.