RSC Advances

RSC Publishing

PAPER

View Article Online
View Journal

A one-pot three-component domino protocol for the synthesis of penta-substituted 4*H*-pyrans†

Cite this: DOI: 10.1039/c3ra41510d

Sathiyamoorthi Sivakumar, Selvaraj Kanchithalaivan and Raju Ranjith Kumar*

Received 27th March 2013,
Accepted 14th May 2013

DOI: 10.1039/c3ra41510d

www.rsc.org/advances

A library of novel 2-(1*H*-indol-3-yl)-6-(methylamino)-5-nitro-4-aryl-4*H*-pyran-3-carbonitriles and 6-(methylamino)-4-(aryl)-5-nitro-2-phenyl-4*H*-pyran-3-carbonitriles were synthesized in excellent yields *via* domino one-pot three-component reactions of 3-(1*H*-indol-3-yl)-3-oxopropanenitrile or benzoylacetonitrile, aromatic aldehydes and (*E*)-*N*-methyl-1-(methylthio)-2-nitroethenamine respectively. This reaction presumably occurs *via* domino Knoevenagel condensation–Michael addition–intramolecular *O*-cyclization sequence of reactions. The significant advantages of this reaction include one-pot process, simple work-up procedure, excellent yields and no column chromatographic purification.

Introduction

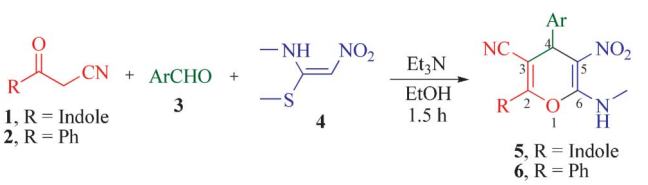
Domino reactions are multi-step processes which allow several bond forming transformations to occur under the same reaction conditions, without the addition of other reagents and catalysts. The subsequent reaction occurs as a result of the functionality formed in the previous step.[1] As these reactions involve multiple processes in one-pot, the need to isolate and purify the intermediates in each step is avoided thereby eliminating the use of large quantity of toxic solvents. Domino reactions are widely accepted by organic chemists world-wide as they increase the synthetic efficiency by reducing the number of laboratory procedures, quantity of chemical and solvents. Incidentally, domino reactions are considered "Green protocols" with respect to atom economy, prevention of waste and avoiding time-consuming purification or protection/de-protection steps.[2] In recent years, investigations pertaining to domino protocols which offer an expedient access to novel heterocycles starting from readily available substrates have gained much of the attention of synthetic organic chemists.[3]

Highly functionalized 4*H*-pyrans constitute a versatile class of organic heterocycles[4] with wide range of biological and chemical applications. These compounds are significant precursors towards the construction of more complex heterocycles and natural products.[5] In this context, a number of methods have been developed for their synthesis, which include step-wise as well as one-pot multi-component reactions. It is pertinent to note that investigations pertaining to the synthesis of 2-amino-4*H*-pyran-3-carbonitrile derivatives from the three-component reactions of malononitrile, aromatic aldehydes and carbonyl compounds have received much attention.[6]

Other reports for the synthesis of 4*H*-pyrans include the DABCO-catalyzed [4 + 2] cycloaddition of β,γ-unsaturated α-ketoesters with allenic esters,[7] nucleophilic addition to electron-deficient 1,3-conjugated enynes in the presence of phase-transfer catalyst,[8] DBU catalyzed reaction of 1-(1-alkynyl)-2-alken-1-ones with 1,3-dicarbonyl compounds,[9] reactions of 1,5-dicarbonyl compounds with Vilsmeier–Haack reagent[10] and $Zn(OAc)_2$-mediated condensation of 1,3-dicarbonyl compounds with aromatic aldehydes.[11]

In the present work, we report the first domino one-pot three-component reactions of 3-(1*H*-indol-3-yl)-3-oxopropanenitrile **1** or benzoylacetonitrile **2**, aromatic aldehydes **3** and (*E*)-*N*-methyl-1-(methylthio)-2-nitroethenamine **4** to afford novel 2-(1*H*-indol-3-yl)-6-(methylamino)-5-nitro-4-aryl-4*H*-pyran-3-carbonitriles **5** and 6-(methylamino)-4-(aryl)-5-nitro-2-phenyl-4*H*-pyran-3-carbonitriles **6** respectively (Scheme 1).

Incidentally, the acetonitriles **1** and **2** are reactive compounds extensively used in domino reactions for the synthesis of divergent heterocycles. For example, 3-pyranyl indoles,[12a] indolyl-pyridines,[12b] two-carbon-tethered 1,3-oxathiazole-indoles,[12c] indolyl-spirooxindoles,[12d] furanylindoles,[12e] naphtho-

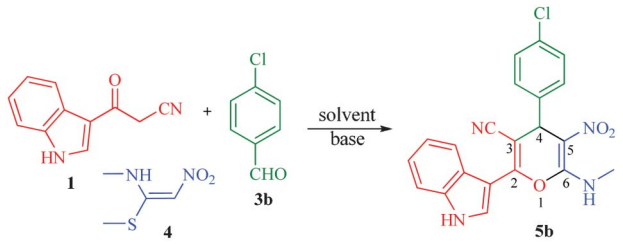


Scheme 1 Synthesis of penta-substituted 4*H*-pyrans **5** and **6**.

Department of Organic Chemistry, School of Chemistry, Madurai Kamaraj University, Madurai-625021, Tamil Nadu, India.
E-mail: raju.ranjithkumar@gmail.com

† Electronic supplementary information (ESI) available: CCDC 911400. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c3ra41510d

Table 1 Optimization of reaction conditions



Entry	Base	Solvent	Time (h)	Yield of **5b**[a]%
1	—	EtOH	8	0[b]
2	Pyridine (1.0)	EtOH	4.5	15
3	Piperidine (1.0)	EtOH	6.5	25
4	Pyrrolidine (1.0)	EtOH	6	25
5	L-Proline (1.0)	EtOH	6	40
6	DABCO (1.0)	EtOH	10	32
7	DBU (1.0)	EtOH	10	30
8	DMAP	EtOH	7	20
9	Et_3N (1.0)	EtOH	1.5	95
10	K_2CO_3 (1.0)	EtOH	12	trace
11	NaOH (1.0)	EtOH	12	trace
12	L-Proline (1.0)	MeOH	6	55
13	Pyrrolidine (1.0)	THF	6	30
14	DMAP (1.0)	neat	6.5	25
15	DABCO (1.0)	neat	5.5	36
16	DBU (1.0)	CH_3CN	6	27
17	Et_3N (1.0)	MeOH	8	50
18	Et_3N (1.0)	2-Propanol	10	42
19	Et_3N (1.0)	THF	8	40
20	Et_3N (1.0)	CH_3CN	8	60

[a] Isolated yield. [b] Product not formed.

pyrans,[13a] fused pyrazolo[3,4-*b*]pyridines, pyrido[2,3-d] pyrimidines,[13b] and thiochromeno[2,3-*b*]pyridines.[13c] Further, it is noteworthy that (*E*)-*N*-methyl-1-(methylthio)-2-nitroethenamine **4** has received much attention recently as versatile intermediate in organic synthesis.[14] It is a crucial intermediate in the synthesis of ranitidine and nizatidine.[15] Moreover, the present work is the first report on the use of **4** in the synthesis of penta-substituted 4*H*-pyran derivatives.

Results and discussion

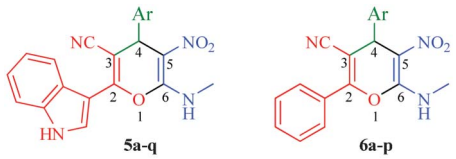
Initially, 3-(1*H*-indol-3-yl)-3-oxopropanenitrile **1**, *p*-chloro-benzaldehyde **3b** and (*E*)-*N*-methyl-1-(methylthio)-2-nitro-ethenamine **4** leading to the formation of 2-(1*H*-indol-3-yl)-6-(methylamino)-5-nitro-4-(4-chlorophenyl)-4*H*-pyran-3-carbonitrile **5b** was chosen as a model substrate to investigate the feasibility of the strategy and to optimize the reaction conditions (Table 1).

To begin with the reaction was performed in the absence of base in ethanol which failed to yield the product even after 8 h either at ambient temperature or reflux conditions (Table 1, entry 1). This reaction was then tested in the presence of bases such as pyridine, piperidine, pyrrolidine, L-Proline, DABCO, DBU and DMAP in refluxing ethanol (Table 1, entries 2–8) but these bases could not promote the reaction efficiently even at prolonged reaction times and poor yields of **5b** were observed (<40%). However, when Et_3N was used as base in refluxing ethanol the reaction completed within 1.5 h with almost quantitative yield of **5b** (95%, Table 1, entry 9). Further, in this case the product is precipitated in the reaction vessel and hence no column chromatographic purification is required. After completion of the reaction the product is filtered and washed with ethanol to obtain pure **5b**. In the presence of potassium carbonate or sodium hydroxide, **5b** was obtained in traces at longer reaction time (Table 1, entries 10 and 11). Then, the test reaction was carried out with common base-solvent pair conditions which are frequently reported in the literature. For example, L-proline-methanol combination afforded a moderate yield of 55% of **5b**, whereas other conditions failed to induce much effect on the reaction and consequently poor yields were observed (Table 1, entries 12–16). From the above results, Et_3N emerged as the ideal choice of base for these domino reactions. Having determined the optimum base for the reaction, investigation pertaining to the choice of an appropriate solvent was performed. The above test reaction was investigated with different solvents such as THF, CH_3CN, MeOH and 2-propanol (Table 1, entries 17–20). From the data in Table 1, ethanol was found to be the ideal solvent for this domino reaction which afforded maximum yield of **5b** (Table 1, entry 9).

The optimal conditions thus established were then applied to the synthesis of a library of novel 2-(1*H*-indol-3-yl)-6-(methylamino)-5-nitro-4-aryl-4*H*-pyran-3-carbonitriles **5a–q** and 6-(methylamino)-4-(aryl)-5-nitro-2-phenyl-4*H*-pyran-3-carbonitriles **6a–p** *via* the one-pot three-component domino reactions of 3-(1*H*-indol-3-yl)-3-oxopropanenitrile **1** or benzoylacetonitrile **2**, aromatic aldehydes **3** and (*E*)-*N*-methyl-1-(methylthio)-2-nitroethenamine **4** respectively (Table 2). A total of thirty three novel 4*H*-pyran-3-carbonitriles **5** and **6** were synthesized in excellent yields apart from 3-pyridine-carboxaldehyde (**6q**) wherein the reaction failed to occur.

The structure of all the 4*H*-pyran-3-carbonitriles **5** and **6** were elucidated with the help of ^1H, ^{13}C and 2D NMR spectroscopy as described for **5f**. In the ^1H NMR spectra of **5f** the singlet at 4.90 ppm can be assigned to H-4 on the basis of its multiplicity. Further, H-4 shows (i) C,H-COSY correlation with carbon signal at 39.7 ppm due to C-4 and (ii) HMBC correlation with carbon signals at 88.9, 106.1, 117.7, 128.6, 133.3, 153.4 and 156.9 ppm which can be assigned to C-3, C-5, nitrile carbon, C-2′′, C-1′′, C-2 and C-6 respectively. From the C,H-COSY spectra H-2′′ appears as a doublet at 7.30 ppm (J = 8.7 Hz) and shows a H,H-COSY correlation with adjacent H-3′′ at 6.87 ppm (J = 8.7 Hz). The methoxy protons appear as a singlet at 3.79 ppm and show a HMBC correlation with C-4′′ at 158.8 ppm. The *N*-CH_3 protons appears as a doublet at 3.31 ppm (J = 4.8 Hz) and show HMBC correlation with C-6 at 156.9 ppm. The H-2′ of indole ring gives a singlet at 7.97 ppm and shows (i) C,H-COSY at 129.5 ppm due to C-2′ and (ii) HMBC correlation with C-3′ at 104.6 ppm, C-3a′ at 124.0 ppm and

Table 2 Three component domino synthesis of **5** and **6**



Comp **5** and **6**	Ar	Yield (%)[a] **5**	Yield (%)[a] **6**	m.p. (°C) **5**	m.p. (°C) **6**
a	C_6H_5	93	93	275–276	240–241
b	4-ClC_6H_4	95	93	293–294	208–209
c	4-FC_6H_4	94	94	286–287	210–211
d	4-BrC_6H_4	93	95	295–296	198–199
e	4-$CH_3C_6H_4$	91	92	289–290	206–207
f	4-$CH_3OC_6H_4$	92	92	270–271	204–205
g	2-ClC_6H_4	92	93	277–278	260–261
h	2-BrC_6H_4	93	92	289–290	254–255
i	2-$CH_3C_6H_4$	91	92	278–279	263–264
j	2-$CH_3OC_6H_4$	92	91	275–276	237–238
k	3-FC_6H_4	91	91	273–274	190–191
l	3-BrC_6H_4	92	92	270–271	237–238
m	3-$O_2NC_6H_4$	93	91	256–257	241–242
n	2,5-$(CH_3O)_2C_6H_3$	93	93	261–262	260–261
o	2,4-$Cl_2C_6H_3$	92	93	299–300	252–253
p	Naphthyl	91	92	260–261	258–259
q	C_5H_4N	91	—[b]	250–251	—[b]

[a] Isolated yield. [b] Product not formed.

C-7a′ at 135.8 ppm. The other protons of indole ring appear as multiplet at 7.22–7.82 ppm whereas the two NH protons appear as broad singlets at 10.34 ppm and 11.75 ppm. The HMBC correlations, ^{1}H and ^{13}C NMR chemical shifts of **5f** are shown in Fig. 1.

Similarly, the structure of **6** was also elucidated unambiguously using ^{1}H, ^{13}C and 2D NMR spectroscopy. The structure of **6** assigned from NMR spectroscopy was further confirmed from the single crystal X-ray studies.[16] The ORTEP diagram of **6d** is shown in Fig. 2. The structure of **6** assigned from NMR spectroscopy and X-ray studies agree well.

A plausible mechanistic pathway for the formation of **5** and **6** is outlined in Scheme 2. Initially, the Knoevenagel condensation between 3-(1*H*-indol-3-yl)-3-oxopropanenitrile **1** or benzoylacetonitrile **2** and aromatic aldehyde **3** affords **8**,[17] which undergoes Michael addition with (*E*)-*N*-methyl-1-

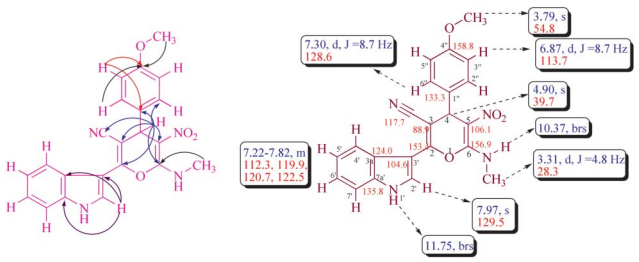


Fig. 1 HMBC's, ^{1}H and ^{13}C NMR chemical shifts of **5f**.

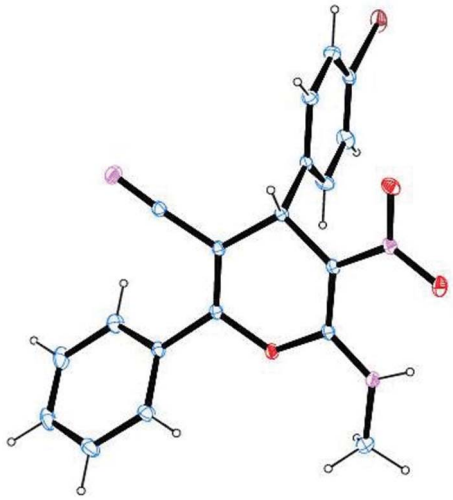
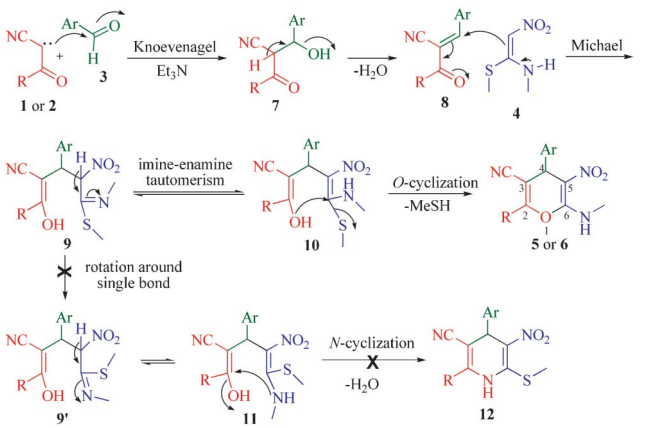


Fig. 2 ORTEP diagram of **6d**.[16]



Scheme 2 Plausible mechanism for the formation of **5** and **6**.

(methylthio)-2-nitroethenamine **4** to give **9**. The intermediate **9** is susceptible to either an intramolecular *O*- or *N*-cyclization which can afford **5**/**6** or the dihydropyridines **12** respectively. However, in the present investigation, 2-(1*H*-indol-3-yl)-6-(methylamino)-5-nitro-4-aryl-4*H*-pyran-3-carbonitriles **5a–q** and 6-(methylamino)-4-(aryl)-5-nitro-2-phenyl-4*H*-pyran-3-carbonitriles **6a–p** were obtained as the sole product, whereas the *N*-cyclized product **12** was not formed even in traces in the course of the reaction. Thus the intermediate **9** undergoes tautomerisation to form **10** followed by *O*-cyclization to form **5** or **6** *via* the elimination of MeSH thereby attributing to the regioselectivity involved in this domino reaction.

Conclusions

The present work reports the one-pot three-component domino reactions for the expedient synthesis of penta-substituted novel 4*H*-pyrans regioselectively in almost quantitative yields. It is noteworthy that this domino reaction results

in the formation of three new bonds (two C–C and one C–O) in a single operation. The important advantages of this methodology include simple and readily available reagents, simple practical work-up and no column chromatographic purification as the product is obtained in pure form just by filtration. Further investigations pertaining to the synthesis of several novel heterocycles using (*E*)-*N*-methyl-1-(methylthio)-2-nitroethenamine are presently under progress.

Experimental section

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 an internal standard and $CDCl_3$ and DMSO-D_6 as a solvents. Standard Bruker software was used throughout the spectral analysis. Chemical shifts are given in parts per million (δ-scale) and the coupling constants are given in Hertz. Elemental analyses were performed on a Perkin Elmer 2400 Series II Elemental CHNS analyzer. Silica gel-G plates (Merck) were used for TLC analysis with a mixture of petroleum ether (60–80 °C) and ethyl acetate as the eluent.

General procedure for the synthesis of 5 and 6

A mixture of 3-(1*H*-indol-3-yl)-3-oxopropanenitrile **1** (1.0 mmol) or benzoylacetonitrile **2** (1.0 mmol), aromatic aldehyde **3** (1.0 mmol) and (*E*)-*N*-methyl-1-(methylthio)-2-nitroethenamine **4** (1.0 mmol) were dissolved in EtOH (10 mL) in a 50 ml round bottom flask. Then Et_3N (1.0 mmol) was added slowly and the reaction mixture was refluxed on a water bath. The consumption of starting material was monitored by TLC. After 90 min the precipitated solid was filtered and washed with cold EtOH (5–7 mL) and dried under vacuum to obtain pure **5** or **6**. The spectroscopic data for compounds **5** and **6** are given below.

2-(1*H*-Indol-3yl)-6-(methylamino)-5-nitro-4-phenyl-4*H*-pyran-3-carbonitrile 5a

Light yellow solid; Yield 93%; mp 275–276 °C; ^{1}H NMR (300 MHz, DMSO-D_6/$CDCl_3$) δ_H: 3.24 (s, 3H, NH–CH_3), 4.90 (s, 1H, Ar–CH), 7.18–7.26 (m, 2H, Ar–H), 7.30–7.32 (m, 1H, Ar–H), 7.36–7.39 (m, 4H, Ar–H), 7.53 (d, 1H, *J* = 7.5 Hz, Ar–H), 7.79 (d, 1H, *J* = 7.5 Hz, Ar–H), 8.02 (s, 1H, Ar–H), 10.41 (brs, N–H), 12.02 (brs, N–H); ^{13}C NMR (75 MHz, DMSO-D_6/$CDCl_3$) δ_C: 28.1, 40.4, 88.1, 104.3, 105.7, 112.0, 117.2, 119.6, 120.4, 122.1, 123.8, 126.9, 127.1, 128.0, 129.1, 135.6, 140.8, 153.5, 156.8: Anal. Calcd for $C_{21}H_{16}N_4O_3$: C, 67.73; H, 4.33; N, 15.05%. Found C, 67.67; H, 4.40; N, 15.12%.

2-(1*H*-Indol-3-yl)-6-(methylamino)-5-nitro-4-(4-chlorophenyl)-4*H*-pyran-3-carbonitrile 5b

Pale yellow solid; Yield 95%; mp 293–294 °C; ^{1}H NMR (300 MHz, DMSO-D_6/$CDCl_3$) δ_H: 3.22 (s, 3H, NH–CH_3), 4.91 (s, 1H, Ar–CH), 7.19–7.24 (m, 2H, Ar–H), 7.41–7.52 (m, 4H, Ar–H), 7.53 (d, 1H, *J* = 6.9 Hz, Ar–H), 7.81 (d, 1H, *J* = 6.6 Hz, Ar–H), 8.10 (s, 1H, Ar–H), 10.41 (brs, N–H), 12.03 (brs, N–H); ^{13}C NMR (75 MHz, DMSO-D_6/$CDCl_3$) δ_C: 28.1, 39.8, 87.4, 104.2, 105.2, 111.9, 117.1, 119.6, 120.4, 122.0, 123.7, 127.9, 128.9, 129.2, 131.8, 135.6, 139.8, 153.6, 156.6: Anal. Calcd for $C_{21}H_{15}ClN_4O_3$: C, 62.00; H, 3.72; N, 13.77%. Found C, 62.07; H, 3.65; N, 13.69%.

2-(1*H*-Indol-3-yl)-6-(methylamino)-5-nitro-4-(4-fluorophenyl)-4*H*-pyran-3-carbonitrile 5c

Yellow solid; Yield 94%; mp 286–287 °C; ^{1}H NMR (300 MHz, DMSO-D_6/$CDCl_3$) δ_H: 3.25 (d, 3H, *J* = 4.5 Hz, NH–CH_3), 4.91 (s, 1H, Ar–CH), 7.11 (t, 2H, *J* = 8.4 Hz, Ar–H), 7.17–7.27 (m, 2H, Ar–H), 7.41 (dd, 2H, *J* = 8.4, 5.4 Hz, Ar–H), 7.53 (d, 1H, *J* = 7.8 Hz, Ar–H), 7.80 (d, 1H, *J* = 7.5 Hz, Ar–H), 8.02 (d, 1H, *J* = 8.1 Hz, Ar–H), 10.40 (d, 1H, *J* = 4.8 Hz, N–H), 12.00 (brs, N–H); ^{13}C NMR (75 MHz, DMSO-D_6/$CDCl_3$) δ_C: 28.1, 39.7, 87.8, 104.3, 105.7, 112.1, 114.6, 114.9, 117.2, 119.6, 120.5, 122.2, 123.8, 128.9, 129.1, 135.7, 136.7, 153.7, 156.8, 162.8: Anal. Calcd for $C_{21}H_{15}FN_4O_3$: C, 64.61; H, 3.87; N, 14.35%. Found C, 64.56; H, 3.94; N, 14.23%.

2-(1*H*-Indol-3-yl)-6-(methylamino)-5-nitro-4-(4-bromophenyl)-4*H*-pyran-3-carbonitrile 5d

Pale yellow solid; Yield 93%; mp 295–296 °C; ^{1}H NMR (300 MHz, DMSO-D_6/$CDCl_3$) δ_H: 3.25 (d, 3H, *J* = 3.6 Hz, NH–CH_3), 4.88 (s, 1H, Ar–CH), 7.16–7.26 (m, 2H, Ar–H), 7.31 (d, 2H, *J* = 7.2 Hz, Ar–H), 7.48–7.52 (m, 3H, Ar–H), 7.80 (d, 1H, *J* = 7.5 Hz, Ar–H), 7.99 (s, 1H, Ar–H), 10.39 (brs, N–H), 11.92 (brs, N–H); ^{13}C NMR (75 MHz, DMSO-D_6/$CDCl_3$) δ_C: 27.9, 39.8, 87.3, 104.0, 105.1, 111.8, 116.8, 119.5, 120.0, 120.2, 121.9, 123.6, 129.1, 130.7, 135.5, 140.1, 153.5, 156.5: Anal. Calcd for $C_{21}H_{15}BrN_4O_3$: C, 55.89; H, 3.35; N, 12.42% . Found C, 55.84; H, 3.44; N, 12.45%.

2-(1*H*-Indol-3-yl)-6-(methylamino)-5-nitro-4-(4-methylphenyl)-4*H*-pyran-3-carbonitrile 5e

Light yellow solid; Yield 91%; mp 289–290 °C; ^{1}H NMR (300 MHz, DMSO-D_6/$CDCl_3$) δ_H: 2.33 (s, 3H, Ar–CH_3), 3.25 (d, 3H, *J* = 4.8 Hz, NH–CH_3), 4.85 (s, 1H, Ar–CH), 7.15–7.27 (m, 6H, Ar–H), 7.53 (d, 1H, *J* = 7.2 Hz, Ar–H), 7.79 (d, 1H, *J* = 7.8 Hz, Ar–H), 7.99 (s, 1H, Ar–H), 10.40 (brs, N–H), 11.93 (brs, N–H); ^{13}C NMR (75 MHz, DMSO-D_6/$CDCl_3$) δ_C: 20.3, 28.1, 40.0, 88.3, 104.3, 105.9, 112.1, 117.3, 119.6, 120.5, 122.2, 123.8, 126.9, 128.6, 128.9, 135.7, 136.4, 137.7, 153.5, 156.8: Anal. Calcd for $C_{22}H_{18}N_4O_3$: C, 68.38; H, 4.70; N, 14.50%. Found C, 68.45; H, 4.62; N, 14.45%.

2-(1*H*-Indol-3-yl)-6-(methylamino)-5-nitro-4-(4-methoxyphenyl)-4*H*-pyran-3-carbonitrile 5f

Yellow solid; Yield 92%; mp 270–271 °C; ^{1}H NMR (300 MHz, DMSO-D_6/$CDCl_3$) δ_H: 3.31 (d, 3H, *J* = 4.8 Hz, NH–CH_3), 3.79 (s, 3H, Ar–OCH_3), 4.90 (s, 1H, Ar–CH), 6.88 (d, 2H, *J* = 8.7 Hz, Ar–H), 7.22–7.27 (m, 2H, Ar–H), 7.30 (d, 2H, *J* = 8.7 Hz, Ar–H), 7.50–7.53 (m, 1H, Ar–H),7.82 (d, 1H, *J* = 7.2 Hz, Ar–H), 7.97 (d, 1H, *J* = 2.7 Hz, Ar–H), 10.37 (brs, N–H), 11.78 (brs, N–H); ^{13}C NMR (75 MHz, DMSO-D_6/$CDCl_3$) δ_C: 28.3, 39.7, 54.8, 88.9, 104.6 106.1, 112.3, 113.7, 117.7, 119.9, 120.7, 122.5, 124.0, 128.6, 129.5, 133.3, 135.8, 153.4, 156.9, 158.4: Anal. Calcd for $C_{22}H_{18}N_4O_4$: C, 65.66; H, 4.51; N, 13.92%. Found C, 65.74; H, 4.45; N, 13.87%.

2-(1*H*-Indol-3-yl)-6-(methylamino)-5-nitro-4-(2-chlorophenyl)-4*H*-pyran-3-carbonitrile 5g

Light yellow solid; Yield 92%; mp 277–278 °C; ^{1}H NMR (300 MHz, DMSO-D_6/$CDCl_3$) δ_H: 3.18 (s, 3H, NH–CH_3), 5.37 (s, 1H, Ar–CH), 7.17–7.27 (m, 2H, Ar–H), 7.30–7.39 (m, 2H, Ar–H), 7.46 (dd, 1H, *J* = 7.2, 1.8 Hz, Ar–H), 7.50–7.55 (m, 2H, Ar–H), 7.79 (d, 1H, *J* = 7.2 Hz, Ar–H), 8.09 (s, 1H, Ar–H), 10.47 (brs, N–H), 12.08 (brs, N–H); ^{13}C NMR (75 MHz, DMSO-D_6/$CDCl_3$) δ_C: 28.1, 38.3, 86.4, 104.2, 104.9, 112.1, 116.9, 119.8, 120.6, 122.3, 123.9, 127.1, 128.8, 129.3, 129.4, 130.5, 132.3, 135.6, 137.7, 153.9, 157.0: Anal. Calcd for $C_{21}H_{15}ClN_4O_3$: C, 62.00; H, 3.72; N, 13.77%. Found C, 61.91; H, 3.61; N, 13.70%.

2-(1*H*-Indol-3-yl)-6-(methylamino)-5-nitro-4-(2-bromophenyl)-4*H*-pyran-3-carbonitrile 5h

Pale yellow solid; Yield 93%; mp 289–290 °C; ^{1}H NMR (300 MHz, DMSO-D_6/$CDCl_3$) δ_H: 3.27 (d, 3H, *J* = 4.8 Hz, NH–CH_3), 5.38 (s, 1H, Ar–CH), 7.14–7.25 (m, 3H, Ar–H), 7.31–7.40 (m, 2H, Ar–H), 7.50 (d, 1H, *J* = 7.8 Hz, Ar–H), 7.56 (d, 1H, *J* = 7.8 Hz, Ar–H), 7.78 (d, 1H, *J* = 8.1 Hz, Ar–H), 7.96 (d, 1H, *J* = 2.7 Hz), 10.44 (d, 1H, *J* = 4.8 Hz, N–H), 11.87 (brs, N–H); ^{13}C NMR (75 MHz, DMSO-D_6/$CDCl_3$) δ_C: 27.9, 40.2, 86.3, 104.1, 105.0, 111.9, 116.5, 119.5, 120.3, 122.0, 122.5, 123.8, 127.4, 128.6, 129.0, 130.2, 132.5, 135.6, 139.1, 153.8, 156.9: Anal. Calcd for $C_{21}H_{15}BrN_4O_3$: C, 55.89; H, 3.35; N, 12.42%. Found C, 56.01; H, 3.41; N, 12.49%.

2-(1*H*-Indol-3-yl)-6-(methylamino)-5-nitro-4-(2-methylphenyl)-4*H*-pyran-3-carbonitrile 5i

Pale yellow solid; Yield 91%; mp 278–279 °C; ^{1}H NMR (300 MHz, DMSO-D_6/$CDCl_3$) δ_H: 2.59 (s, 3H, Ar–CH_3), 3.24 (s, 3H, NH–CH_3), 5.20 (s, 1H, Ar–CH), 7.18–7.25 (m, 6H, Ar–H), 7.52 (d, 1H, *J* = 7.8, Ar–H), 7.79 (d, 1H, *J* = 7.5 Hz, Ar–H), 8.0 (s, 1H, Ar–H), 10.43 (br s, N–H), 11.99 (br s, N–H); ^{13}C NMR (75 MHz, DMSO-D_6/$CDCl_3$) δ_C: 18.3, 27.9, 35.9, 87.9, 104.2, 106.2, 111.8, 116.9, 119.3, 120.3, 121.9, 123.7, 125.9, 126.5, 126.7, 128.6, 129.5, 135.4, 135.6, 139.3, 153.1, 156.8: Anal. Calcd for $C_{22}H_{18}N_4O_3$: C, 68.38; H, 4.70; N, 14.50%. Found C, 68.47; H, 4.64; N, 14.43%.

2-(1*H*-Indol-3-yl)-6-(methylamino)-5-nitro-4-(2-methoxyphenyl)-4*H*-pyran-3-carbonitrile 5j

Light yellow solid; Yield 92%; mp 275–276 °C; ^{1}H NMR (300 MHz, DMSO-D_6/$CDCl_3$) δ_H: 3.20 (s, 3H, NH–CH_3), 3.75 (s, 3H, Ar–OCH_3), 5.04 (s, 1H, Ar–CH), 6.97 (d, 1H, *J* = 7.2, Ar–H), 7.04 (d, 1H, *J* = 8.1, Ar–H), 7.20–7.34 (m, 4H, Ar–H), 7.54 (d, 1H, *J* = 7.2, Ar–H), 7.80 (d, 1H, *J* = 7.2 Hz, Ar–H), 8.08 (s, 1H, Ar–H), 10.47 (brs, N–H), 12.04 (brs, N–H); ^{13}C NMR (75 MHz, DMSO-D_6/$CDCl_3$) δ_C: 28.0, 37.2, 55.2, 86.7, 104.5, 104.9, 111.5, 112.1, 117.5, 119.6, 119.9, 120.5, 122.2, 123.9, 127.5, 128.6, 129.1, 129.9, 135.6, 153.9, 157.1, 157.5: Anal. Calcd for $C_{22}H_{18}N_4O_4$: C, 65.66; H, 4.51; N, 13.92%. Found C, 65.74; H, 4.60; N, 13.88%.

2-(1*H*-Indol-3-yl)-6-(methylamino)-5-nitro-4-(3-fluorophenyl)-4*H*-pyran-3-carbonitrile 5k

Light yellow solid; Yield 91%; mp 273–274 °C; ^{1}H NMR (300 MHz, DMSO-D_6/$CDCl_3$) δ_H: 3.50 (s, 3H, NH–CH_3), 5.27 (s, 1H, Ar–CH), 7.43–7.59 (m, 5H, Ar–H), 7.71–7.79 (m, 1H, Ar–H), 7.87 (d, 1H, *J* = 7.2 Hz, Ar–H), 8.14 (d, 1H, *J* = 7.5 Hz, Ar–H), 8.42 (s, 1H, Ar–H), 10.78 (brs, N–H), 12.42 (brs, N–H); ^{13}C NMR (75 MHz, DMSO-D_6/$CDCl_3$) δ_C: 28.4, 40.2, 87.7, 104.4, 105.3, 112.3, 113.9, 114.1, 114.2, 114.4, 117.5, 120.0, 120.7, 122.5, 123.6, 123.9, 129.7, 130.2, 130.3, 135.8, 144.2, 144.3, 153.7, 156.9, 160.4, 163.6: Anal. Calcd for $C_{21}H_{15}FN_4O_3$: C, 64.61; H, 3.87; N, 14.35% . Found C, 64.57; H, 3.81; N, 14.30%.

2-(1*H*-Indol-3-yl)-6-(methylamino)-5-nitro-4-(3-bromophenyl)-4*H*-pyran-3-carbonitrile 5l

Pale yellow solid; Yield 92%; mp 270–271 °C; ^{1}H NMR (300 MHz, DMSO-D_6/$CDCl_3$) δ_H: 3.51 (s, 3H, NH–CH_3), 5.26 (s, 1H, Ar–CH), 7.50–7.60 (m, 2H, Ar–H), 7.68 (d, 1H, *J* = 7.8 Hz, Ar–H), 7.75 (d, 1H, *J* = 7.8 Hz, Ar–H), 7.83 (d, 1H, *J* = 7.8 Hz, Ar–H), 7.87 (d, 1H, *J* = 7.2 Hz, Ar–H), 7.94 (s, 1H, Ar–H), 8.15 (d, 1H, *J* = 7.2 Hz, Ar–H), 8.43 (s, 1H, Ar–H), 10.78 (brs, N–H), 12.43 (brs, N–H); ^{13}C NMR (75 MHz, DMSO-D_6/$CDCl_3$) δ_C: 28.4, 40.2, 87.5, 104.4, 105.2, 112.3, 117.4, 120.0, 120.7, 121.5, 122.4, 123.9, 126.6, 129.7, 130.1, 130.5, 135.8, 143.9, 153.8, 156.9: Anal. Calcd for $C_{21}H_{15}BrN_4O_3$: C, 55.89; H, 3.35; N, 12.42%. Found C, 55.82; H, 3.29; N, 12.37%.

2-(1*H*-Indol-3-yl)-6-(methylamino)-5-nitro-4-(3-nitrophenyl)-4*H*-pyran-3-carbonitrile 5m

Bright yellow solid; Yield 93%; mp 256–257 °C; ^{1}H NMR (300 MHz, DMSO-D_6/$CDCl_3$) δ_H: 3.32 (d, 3H, *J* = 4.8 Hz, NH–CH_3), 5.09 (s, 1H, Ar–CH), 7.19–7.29 (m, 2H, Ar–H), 7.52 (d, 1H, *J* = 7.8 Hz, Ar–H), 7.60 (t, 1H, *J* = 8.1 Hz, Ar–H), 7.82 (t, 2H, *J* = 7.2 Hz, Ar–H), 8.00 (d, 1H, *J* = 1.8 Hz, Ar–H), 8.15 (d, 1H, *J* = 8.1 Hz, Ar–H), 8.23 (s, 1H, Ar–H), 10.43 (d, 1H, *J* = 4.8 Hz, N–H), 11.80 (brs, N–H); ^{13}C NMR (75 MHz, DMSO-D_6/$CDCl_3$) δ_C: 27.9, 39.9, 86.1, 103.9, 104.7, 111.8, 116.6, 119.3, 120.3, 121.6, 121.7, 121.9, 123.5, 128.9, 133.3, 135.4, 142.5, 147.3, 154.1, 156.4: Anal. Calcd for $C_{21}H_{15}N_5O_5$: C, 60.43; H, 3.62; N, 16.78%. Found C, 60.51; H, 3.70; N, 16.70%.

2-(1*H*-Indol-3-yl)-6-(methylamino)-5-nitro-4-(2,5-dimethoxyphenyl)-4*H*-pyran-3-carbonitrile 5n

Light yellow solid; Yield 93%; mp 261–262 °C; ^{1}H NMR (300 MHz, DMSO-D_6/$CDCl_3$) δ_H: 3.31 (d, 3H, *J* = 5.1 Hz, NH–CH_3), 3.74 (s, 3H, Ar–OCH_3), 3.78 (s, 3H, Ar–OCH_3), 5.00 (s, 1H, Ar–CH), 6.80–6.87 (m, 2H, Ar–H), 6.91 (d, 1H, *J* = 2.7, Ar–H), 7.20–7.28 (m, 1H, Ar–H), 7.51 (d, 1H, *J* = 7.2, Ar–H), 7.62 (s, 1H, Ar–H), 7.81 (d, 1H, *J* = 7.2, Ar–H), 7.93 (d, 1H, *J* = 3.0 Hz, Ar–H), 10.48 (d, 1H, *J* = 4.8 Hz, N–H), 11.57 (brs, N–H); ^{13}C NMR (75 MHz, DMSO-D_6/$CDCl_3$) δ_C: 27.7, 37.4, 54.6, 55.4, 86.0, 104.3, 104.8, 111.7, 111.9, 116.2, 117.1, 119.2, 120.1, 121.8, 123.7, 128.2, 128.4, 135.4, 151.1, 152.3, 153.8, 157.3: Anal. Calcd for $C_{23}H_{20}N_4O_5$: C, 63.88; H, 4.66; N, 12.96%. Found C, 63.95; H, 4.59; N, 12.90%.

2-(1*H*-Indol-3-yl)-6-(methylamino)-5-nitro-4-(2,4-dichlorophenyl)-4*H*-pyran-3-carbonitrile 5o

Yellow solid; Yield 92%; mp 299–300 °C; ^{1}H NMR (300 MHz, DMSO-D_6/$CDCl_3$) δ_H: 3.23 (s, 3H, NH–CH_3), 5.36 (s, 1H, Ar–CH), 7.17–7.27 (m, 2H, Ar–H), 7.38 (dd, 1H, *J* = 8.4, 2.1 Hz, Ar–H), 7.50–7.55 (m, 3H, Ar–H), 7.79 (d, 1H, *J* = 7.5 Hz, Ar–H), 8.04 (s, 1H, Ar–H), 10.47 (brs, N–H), 11.81 (brs, N–H); ^{13}C NMR (75

MHz, DMSO-D_6/$CDCl_3$) δ_C: 28.3, 37.9, 85.7, 104.2, 104.6, 112.2, 116.8, 119.8, 120.6, 122.3, 123.9, 127.2, 128.8, 129.5, 131.7, 132.6, 133.4, 135.7, 136.8, 154.3, 156.9: Anal. Calcd for $C_{21}H_{14}Cl_2N_4O_3$: C, 57.16; H, 3.20; N, 12.70%. Found C, 57.07; H, 3.12; N, 12.65%.

2-(1*H*-Indol-3-yl)-6-(methylamino)-5-nitro-4-(1-naphthyl)-4*H*-pyran-3-carbonitrile 5p

Light yellow solid; Yield 91%; mp 260–261 °C; ^{1}H NMR (300 MHz, DMSO-D_6/$CDCl_3$) δ_H: 3.31 (d, 3H, J = 4.5 Hz, NH–CH_3), 5.89 (s, 1H, Ar–CH), 7.15–7.26 (m, 2H, Ar–H), 7.48–7.52 (m, 3H, Ar–H), 7.56 (d, 1H, J = 7.5 Hz, Ar–H), 7.59–7.65 (m, 1H, Ar–H), 7.78–7.84 (m, 2H, Ar–H), 7.91–7.94 (m, 2H, Ar–H), 8.52 (d, 1H, J = 8.4 Hz, Ar–H), 10.45 (d, 1H, J = 4.5 Hz, N–H), 11.90 (brs, N–H); ^{13}C NMR (75 MHz, DMSO-D_6/$CDCl_3$) δ_C: 27.9, 34.9, 88.3, 104.1, 106.2, 111.7, 116.8, 119.4, 120.1, 121.8, 122.4, 123.7, 124.7, 124.8, 124.9, 125.4, 127.2, 127.7, 128.7, 130.5, 132.6, 135.5, 138.2, 153.2, 156.8: Anal. Calcd for $C_{25}H_{18}N_4O_3$: C, 71.08; H, 4.29; N, 13.26%. Found C, 71.01; H, 4.32; N, 13.21%.

2-(1*H*-Indol-3-yl)-6-(methylamino)-5-nitro-4-(pyridin-3-yl)-4*H*-pyran-3-carbonitrile 5q

Yellow solid; Yield 91%; mp 250–251 °C; ^{1}H NMR (300 MHz, DMSO-D_6/$CDCl_3$) δ_H: 3.25 (d, 3H, J = 4.8 Hz, NH–CH_3), 4.95 (s, 1H, Ar–CH), 7.17–7.27 (m, 2H, Ar–H), 7.34 (dd, 1H, J = 7.5, 4.5 Hz, Ar–H), 7.51 (d, 1H, J = 7.2 Hz, Ar–H), 7.75 (dd, 1H, J = 7.8, 1.5 Hz, Ar–H), 7.82 (d, 1H, J = 7.2 Hz, Ar–H), 8.02 (d, 1H, J = 2.7 Hz, Ar–H), 8.50 (d, 1H, J = 4.5 Hz, Ar–H), 8.66 (s, 1H, Ar–H), 10.41 (d, 1H, J = 4.5 Hz, N–H), 11.92 (brs, N–H); ^{13}C NMR (75 MHz, DMSO-D_6/$CDCl_3$) δ_C: 27.9, 37.9, 86.5, 103.9, 104.8, 111.7, 116.7, 119.3, 120.3, 121.9, 122.8, 123.5, 128.8, 134.4, 135.5, 135.8, 147.8, 148.4, 156.5: Anal. Calcd for $C_{20}H_{15}N_5O_3$: C, 64.34; H, 4.05; N, 18.76%. Found C, 64.41; H, 3.97; N, 18.70%.

6-(Methylamino)-2,4-diphenyl-5-nitro-4*H*-pyran-3-carbonitrile 6a

White solid; Yield 93%; mp 240–241 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 3.24 (d, 3H, J = 5.1 Hz, NH–CH_3), 4.98 (s, 1H, Ar–CH), 7.26–7.37 (m, 5H, Ar–H), 7.47–7.58 (m, 3H, Ar–H), 7.80 (d, 2H, J = 7.8 Hz, Ar–H), 10.08 (brs, N–H); ^{13}C NMR (75 MHz, $CDCl_3$/DMSO-D_6) δ_C: 27.5, 40.6, 92.7, 105.4, 115.4, 126.7, 126.8, 127.0, 127.8, 127.9, 128.2, 131.1, 139.2, 155.2, 156.3. Anal. Calcd for $C_{19}H_{15}N_3O_3$: C, 68.46; H, 4.54; N, 12.61% . Found C, 68.39; H, 4.61; N, 12.54%.

6-(Methylamino)-4-(4-chlorophenyl)-5-nitro-2-phenyl-4*H*-pyran-3-carbonitrile 6b

Light brown solid; Yield 93%; mp 208–209 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 3.23 (d, 3H, J = 5.1 Hz, NH–CH_3), 4.95 (s, 1H, Ar–CH), 7.26–7.35 (m, 4H, Ar–H), 7.47–7.60 (m, 3H, Ar–H), 7.79 (d, 2H, J = 7.8 Hz, Ar–H), 10.09 (brs, N–H); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C: 28.3, 41.1, 93.6, 106.5, 116.2, 127.7, 129.01, 129.04, 129.1, 129.2, 132.2, 132.3, 134.0, 138.2, 138.3, 156.3, 157.4. Anal. Calcd for $C_{19}H_{14}ClN_3O_3$: C, 62.05; H, 3.84; N, 11.43%. Found C, 62.10; H, 3.79; N, 11.34%.

6-(Methylamino)-4-(4-fluorophenyl)-5-nitro-2-phenyl-4*H*-pyran-3-carbonitrile 6c

Light yellow solid; Yield 94%; mp 210–211 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 3.23 (d, 3H, J = 5.1 Hz, NH–CH_3), 4.96 (s, 1H, Ar–CH), 7.04 (t, 2H, J = 8.1 Hz, Ar–H), 7.34 (dd, 2H, J = 8.1, 5.4 Hz, Ar–H), 7.48–7.60 (m, 3H, Ar–H), 7.80 (d, 2H, J = 8.1 Hz, Ar–H), 10.09 (d, 1H, J = 4.8 Hz, N–H); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C: 28.2, 40.9, 93.9, 106.8, 115.7, 115.9, 116.2, 127.7, 129.0, 129.4, 129.6, 132.2, 135.5, 156.2, 157.4. Anal. Calcd for $C_{19}H_{14}FN_3O_3$: C, 64.95; H, 4.02; N, 11.96%. Found C, 64.86; H, 4.09; N, 11.91%.

6-(Methylamino)-4-(4-bromophenyl)-5-nitro-2-phenyl-4*H*-pyran-3-carbonitrile 6d

Light brown solid; Yield 95%; mp 198–199 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 3.23 (s, 3H, NH–CH_3), 4.94 (s, 1H, Ar–CH), 7.24 (dd, 2H, J = 6.9, 1.8 Hz, Ar–H), 7.47–7.59 (m, 5H, Ar–H), 7.77–7.80 (m, 2H, Ar–H), 10.08 (brs, N–H); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C: 28.2, 41.1, 93.2, 106.3, 116.2, 122.1, 127.6, 128.8, 128.9, 129.5, 131.9, 132.2, 138.7, 156.2, 157.3. Anal. Calcd for $C_{19}H_{14}BrN_3O_3$: C, 55.36; H, 3.42; N, 10.19%. Found C, 55.43; H, 3.35; N, 10.25%.

6-(Methylamino)-4-(4-methylphenyl)-5-nitro-2-phenyl-4*H*-pyran-3-carbonitrile 6e

White solid; Yield 92%; mp 206–207 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 2.33 (s, 3H, Ar–CH_3), 3.21 (d, 3H, J = 5.1 Hz, NH–CH_3), 4.95 (s, 1H, Ar–CH), 7.16 (d, 2H, J = 7.8 Hz, Ar–H), 7.24 (d, 2H, J = 7.8 Hz, Ar–H), 7.47–7.55 (m, 3H, Ar–H), 7.79 (d, 2H, J = 7.5 Hz, Ar–H), 10.10 (brs, N–H); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C: 21.1, 28.2, 41.1, 94.2, 106.9, 116.4, 127.6, 127.7, 128.9, 129.2, 129.6, 131.9, 136.7, 137.8, 155.9, 157.5. Anal. Calcd for $C_{20}H_{17}N_3O_3$: C, 69.15; H, 4.93, N, 12.10%. Found C, 69.21; H, 4.86; N, 12.04%.

6-(Methylamino)-4-(4-methoxyphenyl)-5-nitro-2-phenyl-4*H*-pyran-3-carbonitrile 6f

Brown solid; Yield 92%; mp 204–205 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 3.22 (d, 3H, J = 5.1 Hz, NH–CH_3), 3.78 (s, 3H, Ar–OCH_3), 4.92 (s, 1H, Ar–CH), 6.88 (d, 2H, J = 7.5 Hz, Ar–H), 7.27 (d, 2H, J = 7.5 Hz, Ar–H), 7.47–7.57 (m, 3H, Ar–H), 7.79 (d, 2H, J = 6.0 Hz, Ar–H), 10.08 (brs, N–H); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C: 28.2, 40.7, 55.2, 94.1, 106.9, 114.2, 116.5, 127.6, 128.8, 128.9, 129.1, 131.7, 131.9, 155.7, 157.4, 159.3. Anal. Calcd for $C_{20}H_{17}N_3O_4$: C, 66.11; H, 4.72; N, 11.56%. Found C, 66.19; H, 4.64; N, 11.51%.

6-(Methylamino)-4-(2-chlorophenyl)-5-nitro-2-phenyl-4*H*-pyran-3-carbonitrile 6g

White solid; Yield 93%; mp 260–261 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 3.24 (d, 3H, J = 5.1 Hz, NH–CH_3), 5.34 (s, 1H, Ar–CH), 7.25–7.32 (m, 2H, Ar–H), 7.38 (dd, 1H, J = 7.5, 2.1 Hz, Ar–H), 7.43 (dd, 1H, J = 6.9, 2.7 Hz, Ar–H), 7.47–7.59 (m, 3H, Ar–H), 7.78 (dd, 2H, J = 7.8, 1.8 Hz, Ar–H), 10.23 (brs, N–H); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C: 28.2, 40.7, 91.9, 105.8, 115.8, 127.3, 127.8, 129.0, 129.2, 129.5, 130.7, 131.9, 132.1, 133.6, 135.8, 156.7, 157.8. Anal. Calcd for $C_{19}H_{14}ClN_3O_3$: C, 62.05; H, 3.84; N, 11.43%. Found C, 62.11; H, 3.76; N, 11.39%.

6-(Methylamino)-4-(2-bromophenyl)-5-nitro-2-phenyl-4*H*-pyran-3-carbonitrile 6h

White solid; Yield 92%; mp 254–255 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 3.24 (d, 3H, J = 5.1 Hz, NH–CH_3), 5.40 (s, 1H, Ar–CH), 7.17 (t, 1H, J = 7.5 Hz, Ar–H), 7.33 (t, 1H, J = 7.5 Hz, Ar–H), 7.40 (d, 1H, J = 7.5 Hz, Ar–H), 7.48–7.59 (m, 4H, Ar–H), 7.79 (d, 2H, J = 7.8 Hz, Ar–H), 10.23 (brs, N–H); ^{13}C NMR (75 MHz, $CDCl_3$/DMSO-D_6) δ_C: 27.6, 40.7, 90.8, 104.7, 115.0, 122.5, 126.9, 127.1, 128.0, 128.2, 128.7, 130.3, 131.2, 132.6, 137.5, 155.7, 156.5. Anal. Calcd for $C_{19}H_{14}BrN_3O_3$: C, 55.36; H, 3.42; N, 10.19%. Found C, 55.43; H, 3.36; N, 10.27%.

6-(Methylamino)-4-(2-methylphenyl)-5-nitro-2-phenyl-4*H*-pyran-3-carbonitrile 6i

Light yellow solid; Yield 92%; mp 263–264 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 2.67 (s, 3H, Ar–CH_3), 3.25 (d, 3H, J = 5.1 Hz, NH–CH_3), 5.30 (s, 1H, Ar–CH), 7.06–7.09 (m, 1H, Ar–H), 7.15–7.19 (m, 3H, Ar–H), 7.47–7.58 (m, 3H, Ar–H), 7.78 (d, 2H, J = 7.8 Hz, Ar–H), 10.13 (brs, N–H); ^{13}C NMR (75 MHz, $CDCl_3$/DMSO-D_6) δ_C: 18.5, 27.7, 36.4, 92.9, 106.3, 115.7, 126.1, 126.7, 127.0, 128.2, 128.5, 129.9, 131.3, 135.9, 138.3, 155.1, 156.7. Anal. Calcd for $C_{20}H_{17}N_3O_3$: C, 69.15; H, 4.93; N, 12.10%. Found C, 69.22; H, 4.85; N, 12.05%.

6-(Methylamino)-4-(2-methoxyphenyl)-5-nitro-2-phenyl-4*H*-pyran-3-carbonitrile 6j

Light brown solid; Yield 91%; mp 237–238 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 3.22 (d, 3H, J = 5.1 Hz, NH–CH_3), 3.77 (s, 3H, Ar–OCH_3), 5.11 (s, 1H, Ar–CH), 6.89 (d, 1H, J = 8.4 Hz, Ar–H), 6.96 (td, 1H, J = 7.5, 0.9 Hz, Ar–H), 7.25–7.30 (m, 1H, Ar–H), 7.36 (dd, 1H, J = 7.5, 1.5 Hz, Ar–H), 7.46–7.57 (m, 3H, Ar–H), 7.76 (dd, 2H, J = 8.4, 1.8 Hz, Ar–H), 10.26 (brs, N–H); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C: 28.1, 38.7, 55.5, 92.2, 106.2, 111.4, 116.5, 120.9, 126.3, 127.6, 128.9, 129.6, 131.1, 131.8, 156.5, 157.8, 158.3: Anal. Calcd for $C_{20}H_{17}N_3O_4$: C, 66.11; H, 4.72; N, 11.56%. Found C, 66.19; H, 4.64; N, 11.50%.

6-(Methylamino)-4-(3-fluorophenyl)-5-nitro-2-phenyl-4*H*-pyran-3-carbonitrile 6k

Light brown solid; Yield 91%; mp 190–191 °C; ^{1}H NMR (300 MHz, DMSO-D_6) δ_H: 3.13 (s, 3H, NH–CH_3), 4.98 (s, 1H, Ar–CH), 7.15 (t, 1H, J = 8.1 Hz, Ar–H), 7.25–7.30 (m, 2H, Ar–H), 7.42 (dd, 1H, J = 14.4, 8.1 Hz, Ar–H), 7.53–7.64 (m, 3H, Ar–H), 7.84 (d, 2H, J = 7.8 Hz, Ar–H), 10.36 (brs, N–H); ^{13}C NMR (75 MHz, DMSO-D_6) δ_C: 28.2, 40.5, 92.0, 105.0, 114.2, 114.3, 114.4, 114.6, 116.3, 123.8, 127.7, 128.6, 128.8, 130.3, 130.4, 131.7, 143.4, 143.5, 155.9, 156.5, 160.4, 163.6. Anal. Calcd for $C_{19}H_{14}FN_3O_3$: C, 64.95; H, 4.02; N, 11.96%. Found C, 64.87; H, 4.07; N, 11.89%.

6-(Methylamino)-4-(3-bromophenyl)-5-nitro-2-phenyl-4*H*-pyran-3-carbonitrile 6l

White solid; Yield 92%; mp 237–238 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 3.25 (d, 3H, J = 5.1 Hz, NH–CH_3), 4.95 (s, 1H, Ar–CH), 7.21–7.27 (m, 1H, Ar–H), 7.35 (dd, 1H, J = 6.9, 1.5 Hz, Ar–H), 7.43–7.45 (m, 2H, Ar–H), 7.48–7.60 (m, 3H, Ar–H), 7.80 (dd, 2H, J = 8.4, 1.8 Hz, Ar–H), 10.10 (brs, N–H); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C: 28.3, 41.3, 93.3, 106.2, 116.1, 123.0, 126.9, 127.7, 128.9, 129.0, 130.4, 131.4, 132.3, 141.9, 156.4, 157.3: Anal. Calcd for $C_{19}H_{14}BrN_3O_3$: C, 55.36; H, 3.42; N, 10.19%. Found C, 55.45; H, 3.37; N, 10.11%.

6-(Methylamino)-4-(3-nitrophenyl)-5-nitro-2-phenyl-4*H*-pyran-3-carbonitrile 6m

Bright yellow solid; Yield 93%; mp 241–242 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 3.29 (s, 3H, NH–CH_3), 5.13 (s, 1H, Ar–CH), 7.43–7.56 (m, 4H, Ar–H), 7.80–7.82 (m, 3H, Ar–H), 8.16–8.18 (m, 2H, Ar–H), 10.22 (brs, N–H); ^{13}C NMR (75 MHz, $CDCl_3$/DMSO-D_6) δ_C: 27.7, 40.4, 91.2, 104.3, 115.2, 121.7, 121.9, 126.9, 127.9, 129.0, 131.3, 133.4, 141.6, 147.3, 155.8, 155.9: Anal. Calcd for $C_{19}H_{14}N_4O_5$: C, 60.32; H, 3.73; N, 14.81%. Found C, 60.37; H, 3.67; N, 14.78%.

6-(Methylamino)-4-(2,5-dimethoxyphenyl)-5-nitro-2-phenyl-4*H*-pyran-3-carbonitrile 6n

Light yellow solid; Yield 93%; mp 260–261 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 3.24 (d, 3H, J = 5.4 Hz, NH–CH_3), 3.74 (s, 3H, Ar–OCH_3), 3.78 (s, 3H, Ar–OCH_3), 5.05 (s, 1H, Ar–CH), 6.81–6.86 (m, 2H, Ar–H), 6.92 (d, 1H, J = 2.4 Hz, Ar–H), 7.48–7.56 (m, 3H, Ar–H), 7.77 (dd, 2H, J = 8.4, 2.1 Hz, Ar–H), 10.27 (d, 1H, J = 5.1 Hz, N–H): ^{13}C NMR (75 MHz, $CDCl_3$/DMSO-D_6) δ_C: 27.4, 37.8, 54.6, 55.2, 90.4, 104.4, 111.6, 112.2, 115.6, 116.3, 126.8, 127.1, 127.9, 128.6, 130.8, 151.1, 152.4, 155.7, 156.9: Anal. Calcd for $C_{21}H_{19}N_3O_5$: C, 64.12; H, 4.87; N, 10.68%. Found C, 64.19; H, 4.80; N, 10.62%.

6-(Methylamino)-4-(2,4-dichlorophenyl)-5-nitro-2-phenyl-4*H*-pyran-3-carbonitrile 6o

White solid; Yield 93%; mp 252–253 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 3.25 (d, 3H, J = 4.8 Hz, NH–CH_3), 5.30 (s, 1H, Ar–CH), 7.26–7.29 (m, 1H, Ar–H), 7.36–7.40 (m, 2H, Ar–H), 7.52–7.54 (m, 3H, Ar–H), 7.78 (d, 2H, J = 6.3 Hz, Ar–H), 10.19 (brs, N–H);^{13}C NMR (75 MHz, $CDCl_3$) δ_C: 28.3, 40.3, 91.2, 91.4, 105.4, 115.7, 127.6, 127.8, 129.0, 130.5, 132.3, 132.8, 134.3, 134.4, 134.8, 156.9, 157.7: Anal. Calcd for $C_{19}H_{13}Cl_2N_3O_3$: C, 56.73; H, 3.26; N, 10.45%. Found C, 56.67; H, 3.21; N, 10.49%.

6-(Methylamino)-4-(1-naphthyl)-5-nitro-2-phenyl-4*H*-pyran-3-carbonitrile 6p

Bright yellow solid; Yield 92%; mp 258–259 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 3.30 (d, 3H, J = 5.1 Hz, NH–CH_3), 5.91 (s, 1H, Ar–CH), 7.38 (t, 2H, J = 7.2 Hz, Ar–H), 7.43–7.55 (m, 4H, Ar–H), 7.62 (t, 1H, J = 7.5 Hz, Ar–H), 7.76–7.83 (m, 3H, Ar–H), 7.88 (d, 1H, J = 8.4 Hz, Ar–H), 8.45 (d, 1H, J = 8.4 Hz, Ar–H), 10.14 (brs, N–H); ^{13}C NMR (75 MHz, $CDCl_3$/DMSO-D_6) δ_C: 27.7, 35.1, 92.7, 105.9, 115.6, 122.3, 124.8, 125.1, 125.6, 127.0, 127.5, 127.8, 127.9, 128.4, 130.5, 131.0, 132.6, 137.4, 155.1, 156.4. Anal. Calcd for $C_{23}H_{17}N_3O_3$: C, 72.05; H, 4.47; N, 10.96%. Found C, 72.14; H, 4.57; N, 10.87%.

Acknowledgements

RRK thanks the Department of Science and Technology, New Delhi for the funds under (i) DST-SERC Fast Track scheme no. SR/FT/CS-073/2009 and (ii) IRHPA programme for providing high resolution NMR facility. RRK and SS thank the

Sophisticated Analytical Instrument Facility, Indian Institute of Technology Madras for single crystal X-ray diffraction studies. SS thanks the University Grants Commission, New Delhi for the fellowship under UGC-BSR meritorious scheme.

References

1 (*a*) L. F. Tietze and A. Modi, *Med. Res. Rev.*, 2000, **20**, 304; (*b*) L. F. Tietze and N. Rackelmann, *Pure Appl. Chem.*, 2004, **76**, 1967; (*c*) C. de Graaff, E. Ruijter and R. V. A. Orru, *Chem. Soc. Rev.*, 2012, **41**, 3969; (*d*) L. F. Tietze and U. Beifuss, *Angew. Chem., Int. Ed. Engl.*, 1993, **32**, 131; (*e*) L. F. Tietze, *Chem. Ind.*, 1995, **12**, 453; (*f*) L. F. Tietze, *Chem. Rev.*, 1996, **96**, 115; (*g*) L. F. Tietze and M. E. Lieb, *Curr. Opin. Chem. Biol.*, 1998, **2**, 363; (*h*) L. F. Tietze, G. Brasche and K. Gericke, *Domino Reactions in Organic Synthesis*, Wiley-VCH: Weinheim, Germany, 2006.

2 (*a*) S. M. Rajesh, B. D. Bala, S. Perumal and J. C. Menéndez, *Green Chem.*, 2011, **13**, 3248; (*b*) P. Gunasekaran, K. Balamurugan, S. Sivakumar, S. Perumal, J. C. Menéndez and A. I. Almansour, *Green Chem.*, 2012, **14**, 750; (*c*) S. Indumathi, S. Perumal and N. Anbananthan, *Green Chem.*, 2012, **14**, 3361; (*d*) B. D. Bala, S. M. Rajesh and S. Perumal, *Green Chem.*, 2012, **14**, 2484.

3 (*a*) J. M. Khurana, A. Chaudhary, A. Lumb and B. Nand, *Green Chem.*, 2012, **14**, 2321; (*b*) J. Yan, M. Cheng, F. Hu and Y. Hu, *Org. Lett.*, 2012, **14**, 3206; (*c*) X. Yang, S. Li, H. Liu, Y. Jiang and H. Fu, *RSC Adv.*, 2012, **2**, 6549; (*d*) D. C. Kapelle and S. Brase, *ACS Comb. Sci.*, 2011, **13**, 554; (*e*) S. Muthusaravanan, S. Perumal and A. I. Almansour, *Tetrahedron Lett.*, 2012, **53**, 1144; (*f*) D. L. Priebbenow, F. M. Pfeffer and S. G. Stewart, *Eur. J. Org. Chem.*, 2011, 1632.

4 A. J. Phillips, J. A. Henderson and K. L. Jackson, Comprehensive Heterocyclic Chemistry III, *Volume 7: Six-membered Rings with One Heteroatom, and their Fused Carbocyclic Derivatives*, 2008, 7, p. 337.

5 (*a*) R. A. C. Leao, V. D. Pinho, A. S. Coelho, C. D. Buarque, P. F. Moraes, D. A. Alonso, C. Najera and P. R. R. Costa, *Eur. J. Org. Chem.*, 2011, 3313; (*b*) K. C. Nicolaou, D. J. Edmonds and P. G. Bulger, *Angew. Chem., Int. Ed.*, 2006, **45**, 7134; (*c*) B. Stefane, A. Perdih, A. Pevec, T. Solmajer and M. Kocevar, *Eur. J. Org. Chem.*, 2010, 5870; (*d*) M. Li, Y. L. Hou, L. R. Wen and F. M. Gong, *J. Org. Chem.*, 2010, **75**, 8522; (*e*) P. Mishra, H. K. Maurya, B. Kumar, V. K. Tandon and V. J. Ram, *Tetrahedron Lett.*, 2012, **53**, 1056; (*f*) H. K. Maurya, V. K. Tandon, B. Kumar, A. Kumar, V. Huchc and V. J. Ram, *Org. Biomol. Chem.*, 2012, **10**, 605.

6 (*a*) S. Marchalin, B. Baumlova, P. Baran, H. Oulyadi and A. Daich, *J. Org. Chem.*, 2006, **71**, 9114; (*b*) Z. Ye, R. Xu, X. Shao, X. Xu and Z. Li, *Tetrahedron Lett.*, 2010, **51**, 4991; (*c*) N. I. Nikishkin, J. Huskens and W. Verboom, *Eur. J. Org. Chem.*, 2010, 6820; (*d*) W. B. Chen, Z. J. Wu, Q. L. Pei, L. F. Cun, X. M. Zhang and W. C. Yuan, *Org. Lett.*, 2010, **12**, 3132; (*e*) S. Banerjee, A. Horn, H. Khatri and G. Sereda, *Tetrahedron Lett.*, 2011, **52**, 1878; (*f*) Z. P. Hu, C. L. Lou, J. J. Wang, C. X. Chen and M. Yan, *J. Org. Chem.*, 2011, **76**, 3797; (*g*) W. Chen, Y. Cai, X. Fu, X. Liu, L. Lin and X. Feng, *Org. Lett.*, 2011, **13**, 4910; (*h*) S. Khaksar, A. Rouhollahpour and S. M. Talesh, *J. Fluorine Chem.*, 2012, **141**, 11.

7 C. K. Pei, L. Wu, Z. Lian and M. Shi, *Org. Biomol. Chem.*, 2012, **10**, 171.

8 J. Hu, L. Liu, S. Yang and Y. M. Liang, *Org. Biomol. Chem.*, 2011, **9**, 3375.

9 Y. Xiao and J. Zhang, *Chem. Commun.*, 2009, 3594.

10 M. Venugopal, R. Umarani, P. T. Perumal and S. Rajadurai, *Tetrahedron Lett.*, 1991, **32**, 3235.

11 J. Wolinsky and H. S. Hauer, *J. Org. Chem.*, 1969, **34**, 3169.

12 (*a*) N. V. Lakshmi, P. Thirumurugan, K. M. Noorulla and P. T. Perumal, *Bioorg. Med. Chem. Lett.*, 2010, **20**, 5054; (*b*) S. L. Zhu, S. J. Ji, X. M. Su, C. Sun and Y. Liu, *Tetrahedron Lett.*, 2008, **49**, 1777; (*c*) J. Y. Liu, H. Zhang, B. M. Feng, B. Jiang, S. L. Wang and S. J. Tu, *Org. Biomol. Chem.*, 2012, **10**, 5036; (*d*) T. Chen, X. P. Xu and S. J. Ji, *J. Comb. Chem.*, 2010, **12**, 659; (*e*) C. Sun, S. J. Ji and Y. Liu, *Tetrahedron Lett.*, 2007, **48**, 8987.

13 (*a*) X. Tan, B. Liu, X. Li, B. Li, S. Xu, H. Song and B. Wang, *J. Am. Chem. Soc.*, 2012, **134**, 16163; (*b*) Z. Huang, Y. Hu, Y. Zhou and D. Shi, *ACS Comb. Sci.*, 2011, **13**, 45; (*c*) L. R. Wen, Y. J. Shi, G. Y. Liu and M. Li, *J. Org. Chem.*, 2012, **77**, 4252.

14 (*a*) C. Venkatesh, B. Singh, P. K. Mahata, H. Ila and H. Junjappa, *Org. Lett.*, 2005, **7**, 2169; (*b*) Y. Soro, F. Bamba, S. Siaka and J. M. Coustard, *Tetrahedron Lett.*, 2006, **47**, 3315; (*c*) H. S. P. Rao and K. Geetha, *Tetrahedron Lett.*, 2009, **50**, 3836; (*d*) H. S. P. Rao, K. Geetha and M. Kamalraj, *RSC Adv.*, 2011, **1**, 1050; (*e*) M. Mascal and S. Dutta, *Green Chem.*, 2011, **13**, 3101; (*f*) S. Lu, X. Shao, Z. Li, Z. Xu, S. Zhao, Y. Wu and X. Xu, *J. Agric. Food Chem.*, 2012, **60**, 322; (*g*) J. L. Vidaluc, F. Calmel, D. Bigg, E. Carilla, A. Stenger, P. Chopin and M. Briley, *J. Med. Chem.*, 1994, **37**, 689.

15 (*a*) B. J. Price, J. W. Clitherow and J. Bradshaw, *US Patent 4128658*, 1978; (*b*) Z. Han and B. Zhou, *Yiyao Gongye.*, 1986, **17**, 515; (*c*) M. Hohnjec, J. Kuftinec, M. Malnar, M. Skreblin, F. Kajfez, A. Nagln and N. Blazevic, *Analytical Profiles of Drug Substances*, 1986, **15**, 533; (*d*) J. Bradshaw, *Chron. Drug Discovery*, 1993, **3**, 45; (*e*) H. Hinrichsen, A. Halabi, G. Fuhrmann and W. Kirch, *Br. J. Clin. Pharmacol.*, 1993, **35**, 461; (*f*) D. W. Piper and D. Stiel, *J. Gastroenterol. Hepatol.*, 1995, **10**, 205; (*g*) R. K. Gilpin and L. A. Pachla, *Anal. Chem.*, 1997, **69**, 145; (*h*) R. P. Frutos and G. P. Roth, *Bioorg. Med. Chem. Lett.*, 1997, **7**, 3045; (*i*) D. L. Bourdet, K. Lee and D. R. Thakker, *J. Med. Chem.*, 2004, **47**, 2935; (*j*) J. L. Roux, H. Gallard, J. P. Croué, S. Papot and M. Deborde, *Environ. Sci. Technol.*, 2012, **46**, 11095.

16 Crystallographic data (excluding structure factors) for compound 6d has been deposited with the Cambridge Crystallographic Data Center as supplementary publication number CCDC 911400. Copy of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44 (0) 1223 762911 or e-mail: deposit@ccdc.cam.ac.uk].

17 That the domino process involves the formation of intermediate 8 is supported by the isolation of 8 in a separate reaction of 1 or 2 with aromatic aldehyde in the presence of triethylamine under similar reaction conditions. The NMR spectral data of 8 are included in the Electronic Supplementary Information†.

