ISSN 1070-4280, Russian Journal of Organic Chemistry, 2020, Vol. 56, No. 4, pp. 671–678. © Pleiades Publishing, Ltd., 2020.

Microwave-Assisted Three-Component Domino Synthesis of Polysubstituted 4*H*-Pyran Derivatives and Their Anticancer Activity

S. D. Hadiyal[a], N. D. Parmar[b], P. L. Kalavadiya[b], J. N. Lalpara[a], and H. S. Joshi[b,*]

[a] *School of Science, Department of Chemistry, RK University, Rajkot, 360020 Gujarat, India*

[b] *Department of Chemistry, Saurashtra University, Rajkot, 360005 Gujarat, India*

**e-mail: drhsjoshichem@gmail.com*

Received November 21, 2019; revised February 19, 2020; accepted February 20, 2020

Abstract— An efficient microwave-assisted one-pot procedure has been proposed for the synthesis of new 4-aryl-6-(methylamino)-5-nitro-2-(1*H*-pyrrol-2-yl)-4*H*-pyran-3-carbonitriles by condensation of 3-oxo-3-(1*H*-pyrrol-2-yl)propanenitrile with (*E*)-*N*-methyl-1-(methylsulfanyl)-2-nitroethenamine and substituted benzaldehydes in the presence of a catalytic amount of piperidine using ethanol as a solvent. The transformation occurs via successive Knoevenagel condensation, Michael addition, and intramolecular cyclization. The proposed procedure is advantageous due to its one-pot mode, short reaction time, simple purification by recrystallization, and excellent yields. The product structure was confirmed using various spectroscopic techniques, including IR, ^{1}H and ^{13}C NMR, LC/MS, elemental analysis, and single crystal X-ray diffraction study. The synthesized compounds were evaluated for their anticancer activity against 60 different human cancer cell lines in nine cancer panels, and two compounds were found to be potent against different cell lines.

Keywords: 4*H*-pyran, anticancer activity, one-pot synthesis, heteroannulation

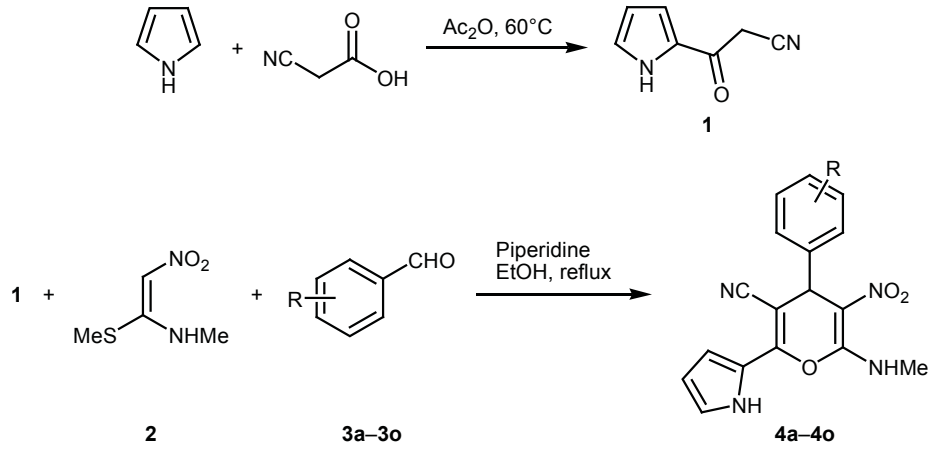
DOI: 10.1134/S1070428020040168

Domino reactions are multi-step processes allowing two or more bond-forming transformations to occur under the same reaction conditions, where each subsequent transformation involves functionalities formed in the previous step; furthermore, neither additional reagents nor catalyst can be added, nor can reaction conditions be changed [1]. Domino reactions are traditionally accepted by organic chemists as universal since they increase the synthetic efficiency by reducing the number of experimental procedures and amounts of chemicals and solvents. Incidentally, domino reactions are considered as a "green protocol" [2] due to atom economy, facile automation, easy workup, prevention of waste, and the absence of purification or protection/deprotection steps [3]. As these reactions involve multiple processes in one pot, there is no need to isolate and purify intermediate products in each step, which eliminates the use of large quantity of toxic solvents.

Polysubstituted 4*H*-pyran derivatives constitute a versatile class of organic heterocycles which are known for their wide range of biological and chemical applications. Compounds containing a 4*H*-pyran moiety have been reported to exhibit anticancer [4], insecticidal [5], anti-inflammatory [6], enzyme inhibitory [7], antimicrobial [8], and antifungal [9] activities; in addition, they are important intermediate products for the construction of pyran-containing heterocycles.

Cancer is the second leading cause of death in the world and is expected to remain the major mortality factor in the future [10]. This is a great concern of the current century to the mankind. As the populations live longer, the negative lifestyle and food habits also increase the cancer risk, so that cancer can also be termed as lifestyle disease [11]. As per the world cancer report released by WHO in the forthcoming years, the mortality rates due to cancer will increase twice its current percentage. So, it is a challenge for the researchers who deal with medicinal chemistry in upcoming with the identification of novel moieties which are useful to design less toxic and highly potent anticancer agents [12]. Despite important advances achieved over recent decades in the research and development of various cancerostatic drugs, current antitumor chemotherapy [13] still suffers from two major limitations. The first one is due to the selectivity

Scheme 1.



R = 4-MeO (**a**), 3,4,5-$(MeO)_3$ (**b**), 4-CN (**c**), 3-F (**d**), 2,4-Cl_2 (**e**), 4-*t*-Bu (**f**), 4-Br (**g**), 4-F (**h**), 3-Br (**i**), 2,4,6-F_3 (**j**), 2,3-Cl_2 (**k**), H (**l**), 4-OH (**m**), 4-F-2-MeO (**n**), 4-Me (**o**).

of conventional chemotherapeutic agents for cancer tissues, bringing about unwanted side effects, and the second one is due to the multiple-drug resistance of cancer cells. Unwanted side effects of antitumor drugs could be overcome with agents capable of discriminating tumour cells [14] from normal proliferative cells, and the resistance could be minimized using combined modality approach with different complementary mechanism of action.

Among the known procedures, the most straightforward method for the synthesis of 4*H*-pyran derivatives includes DABCO-catalyzed [4+2]-cycloaddition of δ-acetoxy allenoates [15]. DBU-catalyzed cyclization of salicylaldehydes with allenic ketones and esters to give the corresponding 2*H*-chromene derivatives [16], reactions of isatin derivatives with kojic acid and active methylene compounds in the presence of $Cu(OTf)_2$ [17], and $InCl_3$-mediated condensation of malononitrile derivatives with various aromatic aldehydes [18] have also been reported.

Herein, we report one-pot three-component domino synthesis of a series of 4-aryl-6-(methylamino)-5-nitro-2-(1*H*-pyrrol-2-yl)-4*H*-pyran-3-carbonitriles as potential anticancer agents. The target compounds **4a**–**4o** were obtained by reacting 3-(1*H*-pyrrol-2-yl)-3-oxopropanenitrile (**1**), (*E*)-*N*-methyl-1-(methylsulfanyl)-2-nitroethen-1-amine (**2**), and various substituted benzaldehydes **3a**–**3o** in the presence of a catalytic amount of piperidine using ethanol as solvent (Scheme 1). Initial 3-oxo-3-(1*H*-pyrrol-2-yl)propanenitrile (**1**) was synthesized by reaction of pyrrole with cyanoacetic acid in acetic anhydride at 60°C. The syntheses of **4a**–**4o** were carried out under conventional heating and microwave irradiation, and the results are compared in Table 1.

In order to optimize the conditions, the microwave-assisted reaction with 4-methoxybenzaldehyde (**3a**) was performed using various solvents and bases at different temperature conditions (Table 2). The best result was obtained in ethanol at 90°C in the presence of piperidine. Halogen-substituted benzaldehydes **3d**, **3e**, and **3g**–**3k** afforded slightly lower yields than those obtained from halogen-free analogs. The formation of all compounds **4a**–**4o** was accelerated by microwave

Scheme 2.

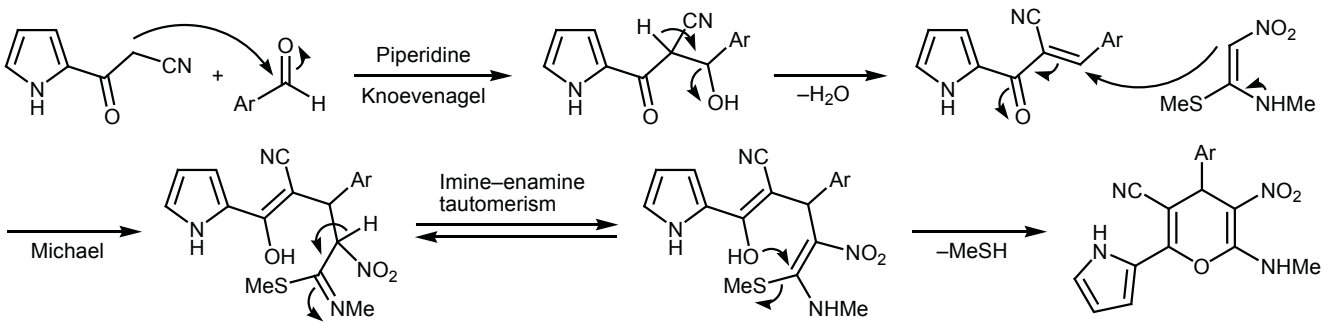


Table 1. Synthesis of 4-aryl-6-(methylamino)-5-nitro-2-(1*H*-pyrrol-2-yl)-4*H*-pyran-3-carbonitriles **4a**–**4o** under microwave irradiation and conventional heating

Comp. no.	R	Microwave irradiation		Conventional heating	
		time, min	yield, %	time, min	yield, %
1a	4-MeO	15	93	120	72
1b	3,4,5-$(MeO)_3$	15	90	120	75
1c	4-CN	15	90	120	70
1d	3-F	15	77	120	65
1e	2,4-Cl_2	20	75	120	67
1f	4-*t*-Bu	15	85	120	71
1g	4-Br	15	76	120	65
1h	4-F	20	71	120	61
1i	3-Br	20	76	120	65
1j	2,4,6-F_3	20	79	120	68
1k	2,3-Cl_2	20	75	120	70
1l	H	20	83	120	70
1m	4-OH	15	79	120	62
1n	2-MeO-4-F	20	93	120	71
1o	4-Me	15	89	120	64

Table 2. Optimization of the reaction conditions

Base	Solvent	Microwave irradiation			Conventional heating		
		temperature, °C	time, min	yield, %	temperature, °C	time, min	yield, %
TEA	EtOH	90	30	70	90	2	65
NaOH/KOH	EtOH	90	30	Traces	90	3.5	Trace
DMAP	EtOH	90	30	30	90	2.1	69
DABCO	EtOH	90	30	40	90	1.5	58
Piperidine	**EtOH**	**90**	**15**	**93**	**90**	**1**	**75**
Piperidine	CH_3CN	85	30	45	85	1.5	35
Piperidine	THF	70	30	70	70	1.7	30
Piperidine	MeOH	70	30	80	70	1.2	71

irradiation, and the products were obtained in shorter time (15–20 min) with higher yields than under conventional heating.

Scheme 2 outlines a plausible mechanism of the three-component condensation. It involves successive Knoevenagel condensation of α-cyano ketone **1** with aromatic aldehyde **3**, Michael addition of nitro enamine **2** to the condensation product, and intramolecular cyclization of the adduct.

The structure of compounds **4a**–**4o** was confirmed by their FT-IR, ^{1}H and ^{13}C NMR, and mass spectra, as well as elemental analyses. The IR spectra of all compounds **4a**–**4o** showed a secondary amine band near 3400 cm^{-1} and a CN stretching band at 2230 cm^{-1}. The ^{1}H NMR spectra of **4a**–**4o** displayed signals in the aromatic region (δ 6–8 ppm) and aliphatic region (δ 3–5 ppm). The CN and C^4 carbon atoms of **4a**–**4o** resonated in the ^{13}C NMR spectra at about δ_C 110 and 83 ppm, respectively. The mass spectra and elemental analyses of all compounds were in agreement with the assigned structures. The structure of **1n** was proved by X-ray analysis (Fig. 1).

The newly synthesized compounds were evaluated for their anticancer activity against 60 human cancer cell lines from nine cancer panels (including CNS cancer, leukemia, renal cancer, non-small-cell lung cancer, colon cancer, melanoma, and ovarian cancer) according to the NCI (National Cancer Institute) methodology. Ten of the synthesized compounds, **4a**–**4c**, **4e**, **4g**, **4h**, and **4k**–**4n** were selected by the National

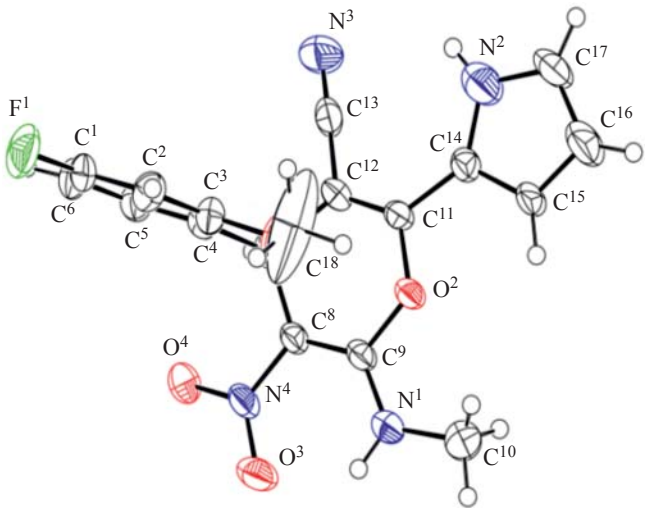


Fig. 1. ORTEP view of the crystal structure of compound **1n**.

Cancer Institute (NCI), and their single-dose response parameters (GI_{50}) were calculated for each NCI-60 cell line. The GI_{50} value corresponds to the concentration causing 50% decrease in net cell growth. Cisplatin (mean GI_{50} value 1.4 mM) was taken as reference drug. Compounds **1a** and **1n** showed a promising anticancer activity due to the presence of *o*- or *p*-methoxy group in their molecules. According to the single-dose response graph, most of the compounds have higher GI_{50} values against CCRF-CEM cell line (leukemia) as compared to other cell lines. Compounds **1a** and **1n** proved to be more potent against leukemia (CCRF-CEM; GI_{50} 43.05 and 17.40, respectively).

EXPERIMENTAL

3-Oxo-3-(1*H*-pyrrol-2-yl)propanenitrile (1). A mixture of 6.7 g (0.1 mol) of pyrrole, and 8.5 g (0.1 mol) of cynoacetic acid in 30 mL of acetic anhydride was heated at 60°C for 5 h, the progress of the reaction being monitored by TLC. When the reaction was complete, the mixture was poured into ice-water and extracted with ethyl acetate, the extract was evaporated, and the residue (brown oil) was triturated with diethyl ether–hexane (1:1) to obtain compound **1** as a brown crystalline solid. Yield 4.4 g (44%), mp 74–76°C. ^{1}H NMR spectrum (400 MHz, $CDCl_3$), δ, ppm: 10.02 s (1H, NH); 7.12 m, 6.93 m, and 6.27 m (1H each, pyrrole); 3.84 s (2H, CH_2).

4-Aryl-6-(methylamino)-5-nitro-2-(1*H*-pyrrol-2-yl)-4*H*-pyran-3-carbonitriles 4a–4o (*general procedure*). *a*. *Microwave-assisted synthesis*. A 30-mL microwave glass vial was charged with 0.2 g (1.0 mmol) of 3-oxo-3-(1*H*-pyrrol-2-yl)propanenitrile (**1**), 1.0 mmol of aromatic aldehyde **3a**–**3o**, 0.12 g (1.0 mmol) of (*E*)-*N*-methyl-1-(methylsulfanyl)-2-nitroethenamine (**2**), and a catalytic amount of piperidine in 10 mL of ethanol. The vial was sealed, placed in a microwave chamber, and irradiated at 90°C with stirring for 15–20 min. After completion of the reaction (TLC), the mixture was cooled to room temperature and poured into ice-cold water (20 mL), and the precipitate was filtered off, washed with cold ethanol (5–7 mL), and dried.

b. *Conventional heating method*. A mixture of 0.2 g (1.0 mmol) of 3-oxo-3-(1*H*-pyrrol-2-yl)propanenitrile (**1**), 1.0 mmol of aromatic aldehyde **3a**–**3o**, 0.14 g (1.0 mmol) of (*E*)-*N*-methyl-1-(methylsulfanyl)-2-nitroethenamine (1.0 mmol), and a catalytic amount of piperidine in 10 mL of ethanol was refluxed for 3 h on an oil bath. The progress of the reaction was monitored by TLC. The mixture was poured into ice-cold water (20 mL), and the precipitate was filtered off, washed with cold ethanol (5–7 mL), and dried under reduced pressure.

4-(4-Methoxyphenyl)-6-(methylamino)-5-nitro-2-(1*H*-pyrrol-2-yl)-4*H*-pyran-3-carbonitrile (1a). Yield 93% (*a*), 72% (*b*); off-white solid, mp 198–200°C. IR spectrum (KBr), ν, cm^{-1}: 3456 (N–H_{aliph}), 3217 (N–H_{arom}), 3140 (C–H_{arom}), 3001, 2947, 2831 (C–H_{aliph}), 2198 (C≡N), 1658 (C=C_{arom}), 1512 (NO_2, asym.), 1473 (δ C–H), 1365 (NO_2, sym.), 1257 (C–O–C, asym.), 1165 (C–N), 1057 (C–O–C, sym.), 817 (δC–H_{arom}), 748, 686 (δC–H). ^{1}H NMR spectrum (400 MHz, $CDCl_3$), δ, ppm: 10.13 s (1H, NH), 9.44 s (1H, *J* = 4.8, N**H**CH_3), 7.26 s (1H, H_{arom}), 7.23 m (1H, H_{arom}), 7.04 t.d (1H, *J* = 2.8, 1.5 Hz, H_{arom}), 6.95 d.d.d (1H, *J* = 4.0, 2.7, 1.5 Hz, H_{arom}), 6.9 m (1H, H_{arom}), 6.85 m (1H, H_{arom}), 6.37 d.t (1H, *J* = 3.9, 2.5 Hz, H_{arom}), 4.90 s (1H, 4-H), 3.78 s (3H, OCH_3), 3.30 d (3H, *J* = 5.2 Hz, NHC**H**$_3$). ^{13}C NMR spectrum (101 MHz, $CDCl_3$), δ_C: 159.46, 157.52, 148.93, 132.14, 128.97, 124.24, 121.37, 118.35, 114.76, 114.40, 111.03, 107.44, 85.37, 58.64, 55.44, 39.74, 28.43. Mass spectrum: *m*/*z* 352 $[M]^+$. Found, %: C 42.70; H 3.07; N 11.04. $C_{18}H_{16}N_4O_4$. Calculated, %: C 42.87; H 3.20; N 11.11.

6-(Methylamino)-5-nitro-2-(1*H*-pyrrol-2-yl)-4-(3,4,5-trimethoxyphenyl)-4*H*-pyran-3-carbonitrile (1b). Yield 90% (*a*), 75% (*b*); off-white solid, mp 206–208°C. IR spectrum (KBr), ν, cm^{-1}: 3449 (N–H_{aliph}), 3317 (N–H_{arom}), 3124 (C–H_{arom}), 3001, 2939, 2831 (C–H_{aliph}), 2206 (C≡N), 1658 (C=C_{arom}), 1504 (NO_2, asym.), 1458 (δC–H), 1334 (NO_2, sym.), 1265 (C–O–C, asym.), 1165 (C–N), 1026 (C–O–C, sym.),

833 (δC–H_{arom}), 771 (δC–H_{arom}), 740, 655 (δC–H). ^{1}H NMR spectrum (400 MHz, DMSO-d_6), δ, ppm: 11.49 s (1H, NH), 10.36 s (1H, J = 4.4, N**H**CH_3), 7.15 d.d (1H, J = 3.6, 4.0 Hz, H_{arom}), 6.96 m (1H, H_{arom}), 6.56 s (2H, H_{arom}), 6.31–6.29 m (1H, H_{arom}), 4.84 s (1H, 4-H), 3.75 s (6H, OCH_3), 3.65 s (3H, OCH_3), 3.24 d (3H, J = 4.8 Hz, NHC**H**$_3$). ^{13}C NMR spectrum (101 MHz, DMSO-d_6), δ_C, ppm: 156.84, 152.94, 149.14, 137.04, 136.96, 123.96, 119.83, 117.64, 114.04, 110.26, 105.21, 104.89, 85.56, 59.91, 55.95, 40.53, 28.67. Mass spectrum: m/z 412 $[M]^+$. Found, %: C 42.28; H 3.41; N 9.72. $C_{20}H_{20}N_4O_6$. Calculated, %: C 42.57; H 3.57; N 9.93.

4-(4-Cyanophenyl)-6-(methylamino)-5-nitro-2-(1*H*-pyrrol-2-yl)-4*H*-pyran-3-carbonitrile (1c). Yield 90% (*a*), 70% (*b*); light yellow solid, mp 224–226°C. IR spectrum (KBr), ν, cm^{-1}: 3433 (N–H_{aliph}), 3371 (N–H_{arom}), 3132 (C–H_{arom}), 3093, 2947 (C–H_{aliph}), 2222 (C≡N), 1658 (C=C_{arom}), 1543 (NO_2, asym.), 1481 (δC–H), 1357 (NO_2, sym.), 1280 (C–O–C, asym.), 1157 (C–N), 1064 (C–O–C, sym.), 833 (δC–H_{arom}), 748, 709 (δC–H). ^{1}H NMR spectrum (400 MHz, DMSO-d_6), δ, ppm: 11.50 s (1H, NH), 10.41 s (1H, J = 4.8, N**H**CH_3), 7.83 d (2H, J = 8.4 Hz, H_{arom}), 7.57 d (2H, J = 8.4 Hz, H_{arom}), 7.17 d (1H, J = 1.2 Hz, H_{arom}), 6.97 s (1H, H_{arom}), 6.30 m (1H, H_{arom}), 4.99 s (1H, 4-H), 3.25 d (3H, J = 4.8 Hz, NCH_3). ^{13}C NMR spectrum (100 MHz, DMSO-d_6), δ_C, ppm: 156.70, 149.47, 147.01, 132.85, 132.60, 128.82, 124.32, 119.63, 118.62, 117.35, 114.35, 110.41, 110.32, 105.16, 84.13, 40.42, 28.73. Mass spectrum: m/z 347 $[M]^+$. Found, %: C 43.27; H 2.54; N 13.96. $C_{18}H_{13}N_5O_3$. Calculated, %: C 43.30; H 2.62; N 14.03.

4-(3-Fluorophenyl)-6-(methylamino)-5-nitro-2-(1*H*-pyrrol-2-yl)-4*H*-pyran-3-carbonitrile (1d). Yield 77% (*a*), 65% (*b*); off-white solid, mp 196–198°C. ^{1}H NMR spectrum (400 MHz, DMSO-d_6), δ, ppm: 11.49 s (1H, NH), 10.39 d (1H, J = 4.8 Hz, N**H**CH_3), 7.55 s (1H, H_{arom}), 7.47 d (1H, J = 7.6 Hz, H_{arom}), 7.33 m (2H, H_{arom}), 7.16 s (1H, H_{arom}), 6.98 s (1H, H_{arom}), 6.30 m (1H, H_{arom}), 4.89 s (1H, 4-H), 3.25 d (3H, J = 5.2 Hz, NHC**H**$_3$). Mass spectrum: m/z 400 $[M]^+$. Found, %: C 59.97; H 3.81; N 16.40. $C_{17}H_{13}FN_4O_3$. Calculated, %: C 60.00; H 3.84; N 16.44.

4-(2,4-Dichlorophenyl)-6-(methylamino)-5-nitro-2-(1*H*-pyrrol-2-yl)-4*H*-pyran-3-carbonitrile (1e). Yield 75% (*a*), 67% (*b*); off-white solid, mp 214–216°C. IR spectrum (KBr), ν, cm^{-1}: 3433 (N–H_{aliph}), 3209 (N–H_{arom}), 3140 (C–H_{arom}), 3024, 2939 (C–H_{aliph}), 2198 (C≡N), 1666 (C=C_{arom}), 1558 (NO_2, asym.), 1473 (δC–H), 1350 (NO_2, sym.), 1280 (C–O–C, asym.), 1180 (C–N), 1064 (C–O–C, sym.), 879 (δC–H_{arom}), 848 (δC–H_{arom}), 817 (C–Cl) 740, 678 (δC–H). ^{1}H NMR spectrum (400 MHz, DMSO-d_6), δ, ppm: 11.52 s (1H, NH), 10.42 d (1H, J = 4.8 Hz, N**H**CH_3), 7.61 d (1H, J = 2.0 Hz, H_{arom}), 7.49 d (1H, J = 8.4 Hz, H_{arom}), 7.42 d.d (1H, J = 8.4, 2.0 Hz, H_{arom}), 7.16 s (1H, H_{arom}), 6.97 s (1H, H_{arom}), 6.31–6.29 m (1H, H_{arom}), 5.32 s (1H, 4-H), 3.25 d (3H, J = 4.8 Hz, NHC**H**$_3$). ^{13}C NMR spectrum (101 MHz, DMSO-d_6), δ_C, ppm: 156.85, 149.65, 137.40, 133.61, 132.82, 132.13, 129.08, 127.83, 124.23, 119.58, 117.08, 114.32, 110.38, 104.89, 83.03, 37.74, 28.69. Mass spectrum: m/z 390 $[M]^+$. Found, %: C 52.13; H 3.02; N 14.30. $C_{17}H_{12}Cl_2N_4O_3$. Calculated, %: C 52.19; H 3.09; N 14.32.

4-(4-*tert*-Butylphenyl)-6-(methylamino)-5-nitro-2-(1*H*-pyrrol-2-yl)-4*H*-pyran-3-carbonitrile (1f). Yield 85% (*a*), 71% (*b*); light green solid, mp 188–190°C. IR spectrum (KBr), ν, cm^{-1}: 3330 (N–H_{aliph}), 3174 (N–H_{arom}), 3140 (C–H_{arom}), 3086, 2943 (C–H_{aliph}), 2202 (C≡N), 1665 (C=C_{arom}), 1540 (NO_2, asym.), 1455 (δC–H), 1334 (NO_2, sym.), 1218 (C–O–C, asym.), 1157 (C–N), 1060 (C–O–C, sym.), 748, 702 (δC–H). ^{1}H NMR spectrum (400 MHz, DMSO-d_6), δ, ppm: 11.47 s (1H, NH), 10.35 d (1H, J = 4.8 Hz, N**H**CH_3), 7.18–7.13 q (5H, J = 8.4 Hz, H_{arom}), 6.94 s (1H, H_{arom}), 6.29 m (1H, H_{arom}), 4.78 s (1H, 4-H), 3.22 d (3H, J = 4.8 Hz, NHC**H**$_3$), 1.29 s (9H, *t*-Bu). Found, %: C 66.61; H 5.79; N 14.76. $C_{21}H_{22}N_4O_3$. Calculated, %: C 66.65; H 5.86; N 14.81.

4-(4-Bromophenyl)-6-(methylamino)-5-nitro-2-(1*H*-pyrrol-2-yl)-4*H*-pyran-3-carbonitrile (1g). Yield 76% (*a*), 65% (*b*); light brown solid, mp 202–204°C. IR spectrum (KBr), ν, cm^{-1}: 3340 (N–H_{aliph}), 3194 (N–H_{arom}), 3086 (C–H_{arom}), 2955, 2916 (C–H_{aliph}), 2214 (C≡N), 1666 (C=C_{arom}), 1550 (NO_2, asym.), 1481 (δC–H), 1365 (NO_2, sym.), 1296 (C–O–C, asym.), 1180 (C–N), 1064 (C–O–C, sym.), 879 (δC–H_{arom}), 740, 678 (δC–H), 578 (C–Br). ^{1}H NMR spectrum (400 MHz, DMSO-d_6), δ, ppm: 11.50 s (1H, NH), 10.39 d (1H, J = 4.8 Hz, N**H**CH_3), 7.55 d (2H, J = 8.4 Hz, H_{arom}), 7.30 d (2H, J = 8.4 Hz, H_{arom}), 7.16 d (1H, J = 1.1 Hz, H_{arom}), 6.97 s (1H, H_{arom}), 6.30 d.t (1H, J = 4.3, 2.3 Hz, H_{arom}), 4.86 s (1H, 4-H), 3.24 d (3H, J = 4.8 Hz, NHC**H**$_3$). ^{13}C NMR spectrum (101 MHz, DMSO-d_6), δ_C, ppm: 156.66, 149.19, 140.93, 131.48, 129.95, 124.17, 120.61, 119.68, 117.49, 114.15, 110.35, 105.51, 84.86, 30.94, 28.69, 22.05, 13.95. Found, %: C 36.81; H 2.31; N 10.10.

$C_{17}H_{13}BrN_4O_3$. Calculated, %: C 36.91; H 2.37; N 10.13.

4-(4-Fluorophenyl)-6-(methylamino)-5-nitro-2-(1*H*-pyrrol-2-yl)-4*H*-pyran-3-carbonitrile (1h). Yield 71% (*a*), 61% (*b*); off-white solid, mp 210–212°C. IR spectrum (KBr), ν, cm^{-1}: 3425 (N–H_{aliph}), 3186 (N–H_{arom}), 3117 (C–H_{arom}), 3032, 2939 (C–H_{aliph}), 2206 (C≡N), 1666 (C=C_{arom}), 1550 (NO_2, asym.), 1473 (δC–H), 1334 (NO_2, sym.), 1280 (C–O–C, asym.), 1165 (C–N), 1064 (C–O–C, sym.), 879 (δC–H_{arom}), 748, 686 (δC–H), 825 (C–F). ^{1}H NMR spectrum (400 MHz, DMSO-d_6), δ, ppm: 11.49 s (1H, NH), 10.37 d (1H, *J* = 5.2 Hz, N**H**CH_3), 7.37 d.d (2H, *J* = 8.4, 5.2 Hz, H_{arom}), 7.20–7.15 m (3H, H_{arom}), 6.97 s (1H, H_{arom}), 6.31–6.30 m (1H, H_{arom}), 4.88 s (1H, 4-H), 3.24 d (3H, *J* = 5.2 Hz, NHC**H**$_3$). ^{13}C NMR spectrum (101 MHz, DMSO-d_6), δ_C, ppm: 162.62, 160.19, 156.67, 149.03, 137.46, 137.43, 129.66, 129.57 123.95, 119.41, 117.52, 115.47, 115.47, 115.26, 114.11, 110.43, 105.73, 85.19, 28.40. Mass spectrum: *m*/*z* 340 $[M]^+$. Found, %: C 59.94; H 3.79 N 16.41. $C_{17}H_{13}FN_4O_3$. Calculated, %: C 60.00; H 3.85; N 16.46.

4-(3-Bromophenyl)-6-(methylamino)-5-nitro-2-(1*H*-pyrrol-2-yl)-4*H*-pyran-3-carbonitrile (1i). Yield 76% (*a*), 75% (*b*); off-white solid, mp 194–196°C. ^{1}H NMR (400 MHz, DMSO-d_6), δ, ppm: 11.49 s (1H, NH), 10.40 d (1H, *J* = 4.8 Hz, N**H**CH_3), 7.55 s (1H, H_{arom}), 7.48 d (1H, *J* = 7.6 Hz, H_{arom}), 7.36–7.30 m (2H, H_{arom}), 7.16 s (1H, H_{arom}), 6.98 s (1H, H_{arom}), 6.31–6.30 m (1H, H_{arom}), 4.89 s (1H, 4-H), 3.25 d (3H, *J* = 5.2 Hz, NHC**H**$_3$). ^{13}C NMR spectrum (101 MHz, DMSO-d_6), δ_C, ppm: 156.70, 149.26, 144.20, 130.78, 130.45, 130.29, 126.94, 124.19, 121.82, 119.70, 117.46, 114.22, 110.37, 105.36, 84.70, 40.04, 28.72. Mass spectrum: *m*/*z* 400 $[M]^+$. Found, %: C 50.81; H 3.24; N 13.91. $C_{17}H_{13}BrN_4O_3$. Calculated, %: C 50.89; H 3.27; N 13.96.

6-(Methylamino)-5-nitro-2-(1*H*-pyrrol-2-yl)-4-(2,4,6-trifluorophenyl)-4*H*-pyran-3-carbonitrile (1j). Yield 79% (*a*), 68% (*b*); off-white solid, mp 202–204°C. ^{1}H NMR spectrum (400 MHz, DMSO-d_6), δ, ppm: 11.61 s (1H, NH), 10.42 d (1H, *J* = 4.0 Hz, N**H**CH_3), 7.26–7.18 m (3H, H_{arom}), 7.01 d (1H, *J* = 3.6 Hz, H_{arom}), 6.33–6.31 m (1H, H_{arom}), 5.32 s (1H, 4-H), 3.25 d (3H, *J* = 5.2 Hz, NHC**H**$_3$). ^{13}C NMR spectrum (101 MHz, DMSO-d_6), δ_C, ppm: 170.90, 159.68, 156.88, 150.31, 124.32, 119.11, 117.21, 114.44, 112.42, 110.60, 103.59, 100.90, 81.30, 59.95, 39.46, 29.90, 28.37, 20.61, 13.88. Mass spectrum: *m*/*z* 376 $[M]^+$. Found, %: C 54.21; H 2.92; N 14.86. $C_{17}H_{11}F_3N_4O_3$. Calculated, %: C 54.26; H 2.95; N 14.89.

4-(2,3-Dichlorophenyl)-6-(methylamino)-5-nitro-2-(1*H*-pyrrol-2-yl)-4*H*-pyran-3-carbonitrile (1k). Yield 75% (*a*), 70% (*b*); off-white solid, mp 206–208°C. IR spectrum (KBr), ν, cm^{-1}: 3430 (N–H_{aliph}), 3215 (N–H_{arom}), 3160 (C–H_{arom}), 2939 (C–H_{aliph}), 2201 (C≡N), 1656 (C=C_{arom}), 1557 (NO_2, asym.), 1473 (δC–H), 1350 (NO_2, sym.), 1271 (C–O–C, asym.), 1182 (C–N), 1065 (C–O–C, sym.), 876 (δC–H_{arom}), 849 (δC–H_{arom}), 810 (C–Cl), 730, 678 (δC–H). ^{1}H NMR spectrum (400 MHz, DMSO-d_6), δ, ppm: 11.52 s (1H, NH), 10.42 d (1H, *J* = 4.8 Hz, N**H**CH_3), 7.61 d (1H, *J* = 2.0 Hz, H_{arom}), 7.49 d (1H, *J* = 8.4 Hz, H_{arom}), 7.42 d.d (1H, *J* = 8.4, 2.0 Hz, H_{arom}), 7.16 s (1H, H_{arom}), 6.97 s (1H, H_{arom}), 6.31–6.29 m (1H, H_{arom}), 5.32 s (1H, 4-H), 3.25 d (3H, *J* = 5.2 Hz, NHC**H**$_3$). Found, %: C 52.13; H 3.03; N 14.28. $C_{17}H_{12}Cl_2N_4O_3$. Calculated, %: C 52.17; H 3.10; N 14.33.

6-(Methylamino)-5-nitro-4-phenyl-2-(1*H*-pyrrol-2-yl)-4*H*-pyran-3-carbonitrile (1l). Yield 83% (*a*), 70% (*b*); dark green solid, mp 206–208°C. IR spectrum (KBr), ν, cm^{-1}: 3340 (N–H_{aliph}), 3186 (N–H_{arom}), 3140 (C–H_{arom}), 3086, 2947 (C–H_{aliph}), 2206 (C≡N), 1666 (C=C_{arom}), 1543 (NO_2, asym.), 1450 (δC–H), 1334 (NO_2, sym.), 1228 (C–O–C, asym.), 1157 (C–N), 1064 (C–O–C, sym.), 748, 702 (δC–H). ^{1}H NMR spectrum (400 MHz, DMSO-d_6), δ, ppm: 11.48 s (1H, NH), 10.37 d (1H, *J* = 4.8 Hz, N**H**CH_3), 7.37–7.26 m (5H, H_{arom}), 7.15 s (1H, H_{arom}), 6.96 s (1H, H_{arom}), 6.30–6.29 m (1H, H_{arom}), 4.85 s (1H, 4-H), 3.25 d (3H, *J* = 4.8 Hz, NHC**H**$_3$). ^{13}C NMR spectrum (101 MHz, DMSO-d_6), δ_C, ppm: 156.78, 149.112, 141.45, 128.62, 127.61, 127.50, 124.05, 119.76, 117.60, 114.02, 110.30, 105.88, 85.56, 40.38, 28.67. Mass spectrum: *m*/*z* 322 $[M]^+$. Found, %: C 63.32; H 4.35; N 17.33. $C_{17}H_{14}N_4O_3$. Calculated, %: C 63.35; H 4.38; N 17.38.

4-(4-Hydroxyphenyl)-6-(methylamino)-5-nitro-2-(1*H*-pyrrol-2-yl)-4*H*-pyran-3-carbonitrile (1m). Yield 79% (*a*), 62% (*b*); brown solid, mp 218–220°C. IR spectrum (KBr), ν, cm^{-1}: 3417 (N–H_{aliph}, O–H), 3271 (N–H_{arom}), 3186 (C–H_{arom}), 3117, and 2978 (C–H_{aliph}), 2206 (C≡N), 1666 (C=C_{arom}), 1512 (NO_2, asym.), 1450 (δC–H), 1365 (NO_2, sym.), 1228 (C–O–C, asym.), 1172 (C–N), 1064 (C–O–C, sym.), 879 (δC–H_{arom}), 748, 702 (δC–H). ^{1}H NMR spectrum (400 MHz, DMSO-d_6), δ, ppm: 11.47 s (1H, NH), 10.34 q (1H, *J* = 4.8 Hz, OH), 9.47 d (1H, *J* = 4.7, N**H**CH_3), 7.15 d.d (1H, *J* = 3.6, 2.4 Hz, H_{arom}), 7.10 d (2H, *J* = 8.4 Hz, H_{arom}), 6.95 s (1H, H_{arom}), 6.73 d (2H, *J* = 8.4 Hz, H_{arom}), 6.30 d.t (1H, *J* = 3.6, 1.6 Hz, H_{arom}), 4.73 s (1H, 4-H), 3.24 d (3H, *J* = 4.8 Hz, NHC**H**$_3$).

Mass spectrum: *m*/*z* 338 $[M]^+$. Found, %: C 60.31; H 4.14; N 16.50. $C_{17}H_{14}N_4O_4$. Calculated, %: C 60.35; H 4.17; N 16.56.

4-(4-Fluoro-2-methoxyphenyl)-6-(methylamino)-5-nitro-2-(1*H*-pyrrol-2-yl)-4*H*-pyran-3-carbonitrile (1n). Yield 93% (*a*), 71% (*b*); light brown solid, mp 170–172°C. IR spectrum (KBr), ν, cm^{-1}: 3371 br (N–H), 3140 (C–H_{arom}), 2947, 2870 (C–H_{aliph}), 2198 (C≡N), 1658 (C=C_{arom}), 1496 (NO_2, asym.), 1465 (δC–H), 1396 (NO_2, sym.), 1280 (C–O–C, asym.), 1172 (C–N), 1057 (C–O–C, sym.), 871 (δC–H_{arom}), 756 (δC–H_{arom}), 725, 648 (δC–H). ^{1}H NMR spectrum (400 MHz, DMSO-d_6), δ, ppm: 11.54 s (1H, NH), 10.39 d (1H, *J* = 5.0, N**H**CH_3), 7.29 d.d (1H, *J* = 8.4, 6.8 Hz, H_{arom}), 7.14 d (1H, *J* = 1.2 Hz, H_{arom}), 6.94–6.91 m (2H, H_{arom}), 6.76 d.t (1H, *J* = 8.4, 2.8 Hz, H_{arom}), 6.28 d.t (1H, *J* = 4.1, 2.2 Hz, H_{arom}), 4.98 s (1H, 4-H), 3.73 s (3H, NHC**H**$_3$), 3.24 s (3H, OCH_3). ^{13}C NMR spectrum (101 MHz, DMSO-d_6), δ_C, ppm: 163.75, 161.33, 158.66, 158.56, 157.49, 149.84, 131.41, 131.31, 123.95, 123.70, 119.93, 117.63, 113.71, 110.14, 106.63, 106.42, 104.93, 100.29, 100.03, 83.80, 56.07, 36.67, 28.50, 26.30. Mass spectrum: *m*/*z* 370 $[M]^+$. Found, %: C 58.34; H 4.01; N 15.10. $C_{18}H_{15}FN_4O_4$. Calculated, %: C 58.38; H 4.08; N 15.13.

The X-ray diffraction data for compound **1n** were obtained from a 0.600×0.560×0.300-mm red block crystal mounted on a glass fiber. All measurements were made on a Rigaku SCX mini diffractometer using graphite monochromatized Mo K_α radiation. Compound **1n** crystallized in triclinic crystal system, space group *P*-1 (Fig. 1). The structure was solved by direct methods and expanded using Fourier techniques. Non-hydrogen and hydrogen atoms were refined anisotropically and by the riding model, respectively, from 9707 observed reflections and 244 variables used for the least-squares refinement and full-matrix final cycle. The maximum and minimum peaks on the final difference Fourier map corresponded to 4.33 and –0.64 $\bar{e}$/Å^3, respectively. The calculations were performed using SHELXL-97 software. The X-ray diffraction data for compound **1n** were deposited to the Cambridge Crystallographic Data Centre (entry no. 1814019).

6-(Methylamino)-4-(4-methylphenyl)-5-nitro-2-(1*H*-pyrrol-2-yl)-4*H*-pyran-3-carbonitrile (1o). Yield 89% (*a*), 64% (*b*); off-white solid, mp 170–172°C. ^{1}H NMR spectrum (400 MHz, DMSO-d_6), δ, ppm: 11.47 s (1H, NH), 10.35 d (1H, *J* = 5.2, N**H**CH_3), 7.15 m (5H, H_{arom}), 6.94 s (1H, H_{arom}), 6.29 m (1H, H_{arom}), 4.78 s (1H, 4-H), 3.22 d (3H, *J* = 4.8 Hz, NHC**H**$_3$), 2.26 s (3H, CH_3). ^{13}C NMR spectrum (101 MHz, DMSO-d_6), δ_C, ppm: 156.78, 148.97, 138.36, 136.85, 129.18, 127.45, 123.99, 119.71, 117.62, 113.97, 110.34, 105.96, 85.71, 56.06, 28.57, 20.58, 18.40. Mass spectrum: *m*/*z* 336 $[M]^+$. Found, %: C 64.23; H 4.75; N 16.61. $C_{18}H_{16}N_4O_3$. Calculated, %: C 64.28; H 4.79; N 16.66.

ACKNOWLEDGMENTS

The authors are thankful to the Department of Chemistry (UGC-SAP, FIST sponsored), Saurashtra University, Rajkot, for providing the laboratory facilities and National Facility for Drug Discovery Complex (NFDD), Centre of Excellence (CoE) and School of Science, Department of Chemistry, RK University, Rajkot (Gujarat), India, for providing the spectral data. The authors are also thankful to the National Cancer Institute, a part of the National Institute of Health (NIH).

CONFLICT OF INTEREST

The authors declare no conflict of interest.

REFERENCES

1. Tietze, L. and Rackelmann, N., *Pure Appl. Chem*., 2004, vol. 76, p. 1967. https://doi.org/10.1351/pac200476111967
2. Martina, K., Tagliapietra, S., Veselov, V., and Cravotto, G., *Front. Chem*., 2019, vol. 7, article no. 95. https://doi.org/10.3389/fchem.2019.00095
3. Rajvan, C., Eelco, R., and Romano, A., *Green Chem*., 2014, vol. 16, p. 2958. https://doi.org/10.1039/C4GC00013G
4. Vidhya, N., Thirumurugan, P., Noorulla, K., and Perumal, P., *Bioorg. Med. Chem. Lett*., 2010, vol. 20, p. 5054. https://doi.org/10.1016/j.bmcl.2010.07.039
5. Manjulla, G., Gupta, M., and Gupta, V., *New J. Chem*., 2015, vol. 39, p. 3578. https://doi.org/10.1039/c4nj02391a
6. Sik, H., Mi, S., Sung, D., Kyoo, M., Ha, D., and Youl, J., *Bioorg. Med. Chem. Lett*., 2010, vol. 20, p. 6569. https://doi.org/10.1016/j.bmcl.2010.09.042
7. Sung, S., Ja, H., Jin, C., and Sup, Y., *Bioorg. Med. Chem. Lett*., 2009, vol. 19, p. 188. https://doi.org/10.1016/j.bmcl.2008.10.119
8. Nazari, P., Bazi, A., Abdulmajid, S., Dolati, H., and Mahbobeh, S., *Iran. J. Pharm. Res*., 2017, vol. 16, p. 943. https://doi.org/10.22037/IJPR.2017.2084
9. Systems, H., Henrikson, J., Ellis, T., King, J., and Cichewicz, H., *Nat. Prod*., 2011, vol. 4, p. 1959. https://doi.org/10.1021/np200454z

10. Christina, M. and Fitzmaurice, D., *JAMA Oncol*., 2017, vol. 3, p. 524. https://doi.org/10.1001/jamaoncol.2016.5688
11. Akbarzadeh, T., Rafinejad, A., Mollaghasem, J.M., Safavi, M., Fallah-Tafti, A., Pordeli, M., Ardestani, S.K., Shafiee, A., and Foroumadi, A., *Arch. Pharm*., 2012, vol. 345, p. 386. https://doi.org/10.1002/ardp.201100345
12. Cragg, G.M., Grothaus, P.G., and Newman, D.J., *Chem. Rev*., 2009, vol. 109, p. 3015. https://doi.org/10.1021/cr900019j
13. Xumeng, W., Xuanrong, S., Zhiqian, G., Jianbin, T., Youqing, S., Tony, D., He, T., and Weihong, Z., *J. Am. Chem. Soc*., 2014, vol. 136, p. 3579. https://doi.org/10.1021/ja412380j
14. Veri, C., Gorlatov, S., Burke, H., Johnson, S., Stavenhagen, S., and Koenig, J., *Immunology*, 2007, vol. 121, p. 392. https://doi.org/10.1111/j.1365-2567.2007.02588.x
15. Gu, Y., Li, F., Hu, P., Liao, D., and Tong, X., *Org. Lett*., 2015, vol. 17, p. 1106. https://doi.org/10.1021/acs.orglett.5b00359
16. Zhao, G., Shi, Y., and Shi, M., *Org. Lett*., 2005, p. 3057. https://doi.org/10.1021/ol051920v
17. Parthasarathy, K., Praveen, C., Balachandran, C., Senthil, P., Ignacimuthu, S., and Perumal, P., *Bioorg. Med. Chem. Lett*., 2013, vol. 23, p. 2708. https://doi.org/10.1016/j.bmcl.2013.02.086
18. Shanthi, G., Subbulakshmi, G., and Perumal, P., *Tetrahedron*, 2007, vol. 63, p. 2057. https://doi.org/10.1016/j.tet.2006.12.042