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One-pot synthesis of unsymmetrical biaryls from suitably functionalized 2*H*-pyran-2-ones through carbanion-induced ring-transformation reactions

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An innovative synthesis of unsymmetrical biaryls (**2**,**6**) with electron-acceptor and electron-donor substituents through carbanion-induced C–C bond formation from 6-aryl-3-cyano-4-methylthio-2*H*-pyran-2-ones (**1**) and 4-*sec*-amino-6-aryl-2*H*-pyran-2-ones (**5**), using aliphatic ketones as a source of carbanion, is delineated and illustrated. However, a reaction of pyran-2-ones (**1**) with aromatic ketones failed to yield any desired product and *in lieu* a new compound isolated was characterized as the corresponding (4,6-diarylpyran-2-ylidene)acetonitrile (**3**). The structure of two representative compounds **5h** and **6q** has been confirmed by single-crystal X-ray diffraction analysis.

Introduction

The synthesis of highly functionalized biaryl systems, particularly those with hindered rotation, is highly demanding not only in the construction of natural products and pharmaceuticals, but also in the discovery of entities for asymmetric synthesis,[1] crown ethers,[2] chiral liquid crystals,[3] chiral phases for chromatography[4] and preparation of materials for their nonlinear optical properties.[5]

Historically, biaryls have been synthesized by coupling of two aromatic moieties in the presence of different coupling reagents.[6–13] Recently, palladium-catalyzed cross-coupling between electrophilic (Ar-X) and organometallic species prepared from Mg, Zn, Sn and B was found to be a versatile route for C–C bond formation.[14–16] Though palladium-catalyzed coupling between arylboronic acids and haloarenes is highly versatile for the synthesis of biaryls[17] it suffered from certain limitations due to coupling between the arylboronic acid with a phenyl group of triphenylphosphine as well as self-coupling of aryl groups of the arylboronic acid. However, initially, unsymmetrical biaryls were synthesized[18] by Diels–Alder reactions of 2*H*-pyran-2-ones with electron-rich and -poor dienophiles. Further, Gompper and Christmann[19] have also prepared similar compounds from the reaction of 2*H*-pyran-2-one with aryl Grignard reagents. The recent efficient synthesis of unsymmetrical biaryls, through oxazoline-mediated coupling reactions,[20] though it acquired widespread popularity and applications in natural-product synthesis has limitations with respect to certain substitution in the phenyl ring and the difficulty in obtaining numerous Grignard reagents. The continuously growing demands for functionalized biaryls warrants an efficient and convenient, innovative route for their synthesis.

Results and discussion

Our approach to the synthesis of unsymmetrical biaryls with electron-donor and -acceptor substituents is based on the base-catalyzed ring-transformation reactions of 6-aryl-3-cyano-4-methylthio-2*H*-pyran-2-ones **1** and 4-*sec*-amino-6-aryl-3-cyano-2*H*-pyran-2-ones **5** separately. The precursors **1** were prepared from base-catalyzed reaction of ethyl 2-cyano-3,3-bis(methylthio)acrylate and aryl ketones as described earlier.[21] A further reaction of **1** with secondary amines such as piperidine, morpholine and piperazine, *etc.* at reflux temperature in ethanol led to 4-*sec*-aminopyran-2-ones **5** (Schemes 1 and 2).

The structure of all the synthesized compounds was confirmed on the basis of spectroscopic data and elemental analyses. The NMR spectrum of **5a** showed two triplets at δ 3.42 and 4.07 due to four methylene protons of the piperazinyl moiety. A singlet at δ 6.42 was assigned as a characteristic peak for the C5 proton in the pyran-2-one (**1** and **5a**). Three multiplets at δ 6.85–6.95, 7.22–7.36 and 7.59–7.71 were designated for aromatic protons. In all the compounds a characteristic peak for the C5 proton at $\delta \approx 6.42$ clearly indicated the presence of the lactone ring. In addition a peak at $\nu \approx 1689$ cm^{-1}, due to the carbonyl function in the IR spectrum, confirmed the presence of the lactone ring in compounds **5**. The structure of **5h** was finally ascertained by single-crystal X-ray diffraction analysis. The presence of the the piperazinyl moiety at C4 in the crystal structure of **5h** (Fig. 1) confirmed the nucleophilic substitution by piperazine only at the 'soft' electrophilic centre C4 of the lactone ring. The molecular structure of **5h** (Fig. 1) showed that the piperazine ring (B) adopts a chair conformation [deviations of N7 and N10 are −0.604(5) and 0.704(4) Å from the mean plane defined by C8, C9, C11 and C12] and the N7 and N10 substituents are in equatorial positions. The fluorobenzene rings (C and D) are separated from each other by an angle of 107.9(2)° at C13. The chlorobenzene ring (E) is almost in the same plane as the lactone ring (A) [twist angle is 5.8(1)°]. There is an intramolecular H-bond, C31–H31···O1, with H-bonding parameters C31–O1: 2.708(4) Å, H31···O1: 2.376 Å and C31–H31···O1: 101.4°.

The crystal packing (Fig. 2) revealed a network of various weak intermolecular H-bonds and aromatic π–π interactions (APPIs). Currently the importance of these interactions is being realized in crystal engineering[22] and supramolecular design.[23] The weak H-bonding of the types C–H···O, C–H···N and C–H···F range in length from 3.243 to 3.799 Å (some of the H-bonds are shown in Fig. 2 by dotted lines). Both the chlorobenzene (E) and lactone (A) rings are stacked in

† For X-ray crystallography queries.

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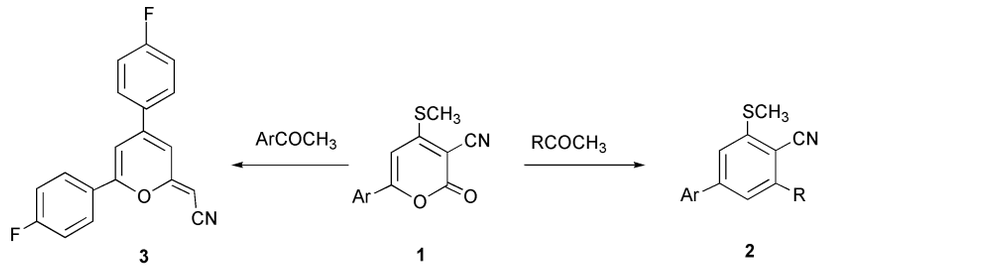
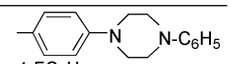
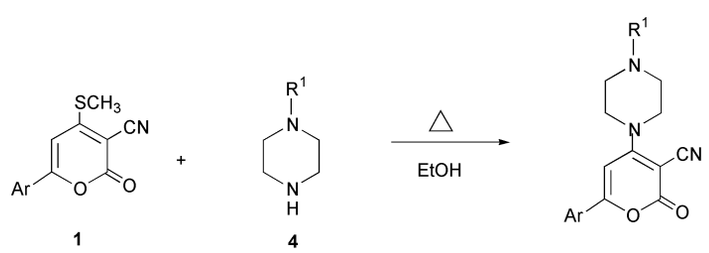


3 1 2

1	Ar
a	4-FC_6H_4
b	4-ClC_6H_4
c	3,4-$F_2C_6H_3$
d	3,4-$Cl_2C_6H_3$
e	2-F,4-$CH_3OC_6H_3$
f	2-Furyl

2	R	Ar
a	CH_3	
b		4-FC_6H_4
c		4-ClC_6H_4
d	C_2H_5	4-ClC_6H_4

Scheme 1



1 4 5

5	R^1	Ar
a	C_6H_5	4-FC_6H_4
b	2-$CH_3OC_6H_4$	4-FC_6H_4
c	2-Pyridyl	4-FC_6H_4
d	HC(4-ClC_6H_4)C_6H_5	4-FC_6H_4
e	C_6H_5	3,4-$F_2C_6H_3$
f	HC(4-ClC_6H_4)C_6H_5	3,4-$F_2C_6H_3$
g	C_6H_5	4-ClC_6H_4
h	HC(4-FC_6H_4)$_2$	4-ClC_6H_4
i	2-$CH_3OC_6H_4$	4-ClC_6H_4
j	2-Pyridyl	4-ClC_6H_4
k	HC(4-ClC_6H_4)C_6H_5	4-ClC_6H_4
l	$CH_2C_6H_5$	4-ClC_6H_4
m	C_6H_5	2,4-$Cl_2C_6H_3$
n	C_6H_5	2-F,4-$CH_3OC_6H_3$
o	HC(4-FC_6H_4)$_2$	Furyl

Scheme 2

pairs due to APPI. The molecules are stacked in such a way that ring A overlaps with ring B and *vice-versa* (as indicated by shading in Fig. 2) along the *b*-axis direction. An approximate interplanar distance of 3.8 Å separates the stacked rings. In addition, one of the fluorobenzene rings, D, also shows APPI (with an approximate stacking distance of 3.7 Å) in an offset geometry with its symmetry-related counterpart (as indicated by ↔ in Fig. 2). These π–π interactions are in accord with Hunter's electrostatic model.[24] Thus the combination of weak H-bonding and aromatic π–π interactions stabilizes the molecule in the crystalline state.

Based on the topography of pyran-2-ones **1** and **5**, they may be considered as cyclic ketene hemithioacetals (**1**) and ketene hemiaminals (**5**) with three electrophilic centres C2, C4 and C6 in which the last is highly susceptible to nucleophilic attack, owing to extended conjugation and the presence of an electron-withdrawing substituent at position 3 in the pyran ring. The difference in electron density on various carbon centres led us to exploit pyran-2-ones **1** and **5** as synthons for ring-transformation reactions. Thus the carbanion generated *in situ* from an aliphatic ketone by alkali in DMF attacks at C6 with ring opening followed by decarboxylation and condensation–cyclization involving both the keto group and C3 of the pyran ring with elimination of water, affording products **2** and **6** (Schemes 1 and 3). This is a one-pot reaction in which an equimolar mixture of a pyran-2-one (**1** or **5**), aliphatic ketone, and powdered KOH in DMF was stirred at ambient temperature for 35 h under an inert atmosphere. After pouring of the reaction mixture into ice–water, the solution was neutralized with 10% HCl to pH 7, the precipitate thus obtained was filtered off, and the crude product was purified by column chromatography as an unsymmetrical biaryl **2** or **6**. This procedure not only provided a novel general route for preparing highly functionalized unsymmetrical biaryls but also opens an alternative approach to the synthesis of polyfunctionalized *N*,*N*′-diarylpiperazines as drug intermediates.

A plausible mechanism of this reaction is depicted in Scheme 3. The ^{1}H NMR spectrum of a biaryl, 4-(4-chlorophenyl)-2-

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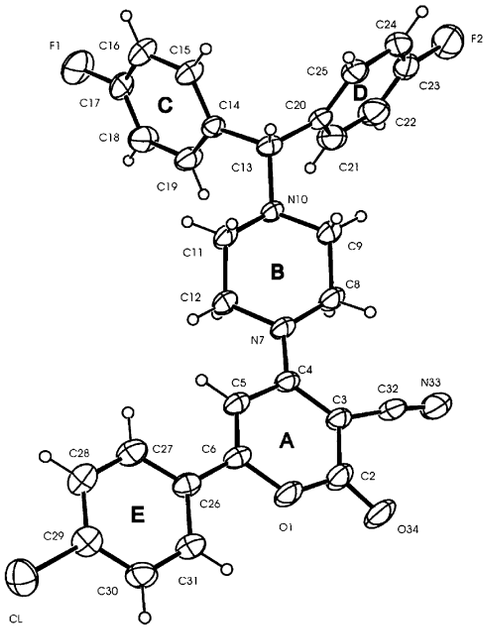

Fig. 1 ORTEP diagram showing the molecular structure of **5h** with atom labelling.

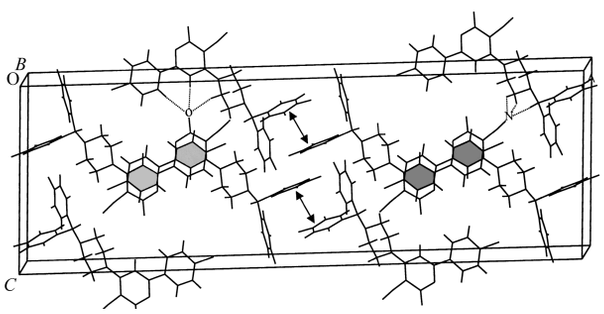

Fig. 2 PLUTO diagram showing the crystal-packing interactions of **5h**.

methyl-6-(4-phenylpiperazinyl-1-yl)benzonitrile **6g**, showed a singlet at δ 2.59 for a methyl group and two triplets at δ 3.40 and 4.06 for piperazinyl protons. A singlet at δ 6.42 was assigned for two aromatic protons. Three doublets at δ 6.96, 7.46 and 7.76 were assigned to two aromatic protons each while a multiplet at δ 7.27–7.33 corresponded to 3 aromatic protons. The structure of another representative compound, **6q**, was confirmed by single-crystal X-ray analysis. It is evident from its crystal structure (Fig. 3) that it has been formed by attack of a carbanion, a 'hard' base generated from the ketone, at the C6 position of the lactone ring, followed by condensation. The crystal structure of **6q** showed that the asymmetric unit contains two molecules of similar conformations (not shown). The piperazine ring (C) adopts a chair conformation [deviations of N16 and N19 are 0.600(4) and −0.699(4) Å from the mean plane defined by C17, C18, C20 and C21 atoms in one molecule and those of N46 and N49 are 0.716(4) and −0.568(4) Å from the mean plane defined by C47, C48, C50 and C51 atoms in the other molecule]. The structure further shows that ring B is twisted with respect to ring A by an angle 36.6(1)° for one molecule and 38.1(1)° for the other molecule in the asymmetric unit.

The crystal packing revealed the presence of weak intra- and intermolecular C–H · · · N and C–H · · · π interactions that play a fundamental role in three-dimensional organization of the molecules in the solid state.[25] The C–H · · · N distances range from 3.418 to 3.762 Å while the C–H · · · π distances are 2.916(3) and 2.942(5) Å respectively.

Our synthetic approach in many ways is superior to the existing procedures known for the construction of unsymmetrical

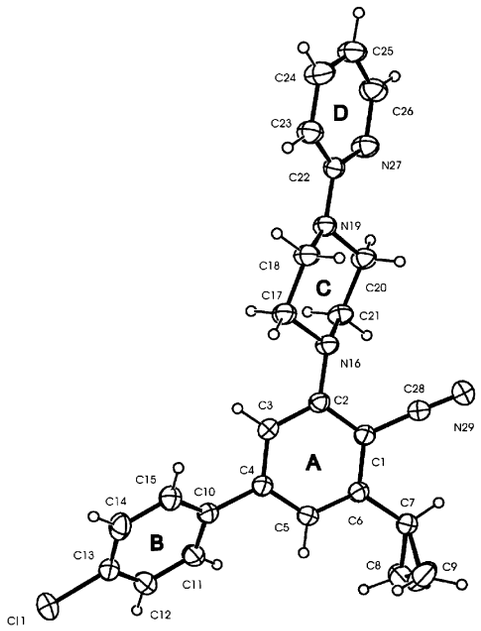

Fig. 3 ORTEP diagram showing the molecular structure of **6q** with atomic labelling.

biaryls with respect to its (i) mild reaction conditions, (ii) use of inexpensive reactants, (iii) no use of catalyst in the reaction, (iv) versatility and compatibility, and (v) easy access to the synthesis of 1,4-biarylpiperazines.

Exploring further the versatility of this reaction, alkyl aromatic ketones were used as a source of carbanions but failed to yield desired products, and instead a new compound isolated from the reaction with *p*-fluoroacetophenone was identified as the (4,6-diarylpyran-2-ylidene)acetonitrile **3** through enolization of the alkyl aryl ketone followed by cyclization (Scheme 1).

Experimental

Mps were determined in an open capillary Büchi-530 melting point apparatus and are uncorrected. ^{1}H NMR spectra were recorded on Bruker WM (400 MHz) and Bruker WM (200 MHz) spectrometers using $SiMe_4$ as reference compound. IR spectra were obtained in KBr discs on a Perkin-Elmer Ac-1 spectrophotometer. Electron-impact mass spectra were obtained at 70 eV using a JEOL JMS-D 300 spectrometer. Elemental analyses (C, H, N) were carried out on a Carlo Erba EA-1108 elemental analyzer, within ±0.5% of the theoretical values. Thin layer chromatography (TLC) was performed on 7 × 3 cm precoated analytical plates (SRL).

General procedure for the synthesis of 2a–d and 3

A mixture of a 6-aryl-3-cyano-4-methylthio-2*H*-pyran-2-one **1** (10 mmol), ketone $RCOCH_3$ (15 mmol) and potassium hydroxide (15 mmol) in dry DMF was stirred at room temperature under a nitrogen blanket for 30 h. The reaction mixture was then poured into ice–water and vigorously stirred for 30 min and thereafter acidified with 10% HCl. The precipitate obtained was filtered off, washed with water, and purified on a silica gel column, using chloroform–hexane (1 : 1) as eluent.

2-Methyl-6-methylthio-4-[4-(4-phenylpiperazino)phenyl]-benzonitrile 2a. Yield 60%; mp 210 °C; ν_{max}/cm^{-1} 2204 (CN); *m*/*z* (EI) 399 (M^+, 100%), 384 (10.2), 307 (20.6); δ_H (200 MHz; $CDCl_3$) 1.89 (s, 3H, CH_3), 2.56 (s, 3H, SCH_3), 3.25–3.44 (m, 8H, NCH_2), 6.87 (s, 2H, CH), 6.97–7.10 (m, 5H, ArH), 7.25–7.34 (m, 4H, ArH) (Found: C, 75.29; H, 6.42; N, 10.39. $C_{25}H_{25}N_3S$ requires C, 75.15; H, 6.31; N, 10.52%).

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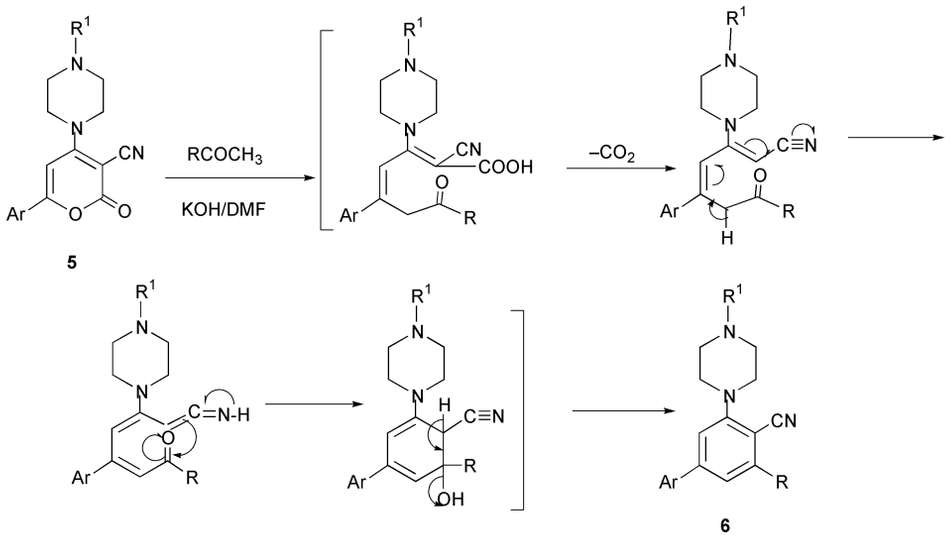
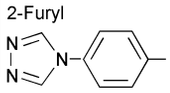


6	R	R^1	Ar
a	CH_3	C_6H_5	4-FC_6H_4
b	CH_3	2-$CH_3OC_6H_4$	4-FC_6H_4
c		2-$CH_3OC_6H_4$	4-FC_6H_4
d		2-Pyridyl	4-FC_6H_4
e	CH_3		4-FC_6H_4
f	C_2H_5	HC(4-ClC_6H_4)C_6H_5	4-FC_6H_4
g	CH_3	2-Pyridyl	4-ClC_6H_4
h	CH_3	C_6H_5	4-ClC_6H_4
i	CH_3	HC(4-ClC_6H_4)C_6H_5	4-ClC_6H_4
j	CH_3	HC(4-FC_6H_4)$_2$	4-ClC_6H_4
k	CH_3	2-$CH_3OC_6H_4$	4-ClC_6H_4
l	$(CH_2)_2C_6H_5$	2-Pyridyl	4-ClC_6H_4
m	$(CH_2)_4CH_3$	2-$CH_3OC_6H_4$	4-ClC_6H_4
n	$(CH_2)_2C_6H_5$	HC(4-FC_6H_4)$_2$ HC(4-FC_6H_4)$_2$	4-ClC_6H_4
o		2-$CH_3OC_6H_4$	4-ClC_6H_4
p		$CH_2C_6H_5$	4-ClC_6H_4
q		2-Pyridyl	4-ClC_6H_4
r		HC(4-FC_6H_4)$_2$	4-ClC_6H_4
s	CH_3	C_6H_5	2,4-$Cl_2C_6H_3$
t	CH_3	HC(4-FC_6H_4)$_2$	2-Furyl
u		HC(4-FC_6H_4)$_2$	2-Furyl
v	CH_3	Pyrimidin-4-yl	

Scheme 3

2-Cyclopropyl-4-(4-fluorophenyl)-6-(methylthio)benzonitrile 2b. Yield 38%; mp 115 °C; ν_{max}/cm^{-1} 2229 (CN); *m*/*z* (EI) 284 (M^+ + 1, 75%), 283 (M^+, 52.4), 154 (100); δ_H (200 MHz, $CDCl_3$) 0.84 (q, 2H, *J* 5.2 Hz, CH_2), 1.15 (q, 2H, *J* 5.4 Hz, CH_2), 1.67–2.32 (m, 1H, CH), 2.60 (s, 3H, SCH_3), 6.82 (s, 2H, CH), 7.05–7.19 (m, 2H, ArH), 7.46–7.53 (m, 2H, ArH) (Found: C, 71.56; H, 4.85; N, 4.99. $C_{17}H_{14}FNS$ requires C, 71.89; H, 4.96; N, 4.94%).

4-(4-Chlorophenyl)-2-cyclopropyl-6-(methylthio)benzonitrile 2c. Yield 58%; mp 122 °C; ν_{max}/cm^{-1} 2229 (CN); *m*/*z* (EI) 299 (M^+, 100%), 286 (60.2), 249 (43.1); δ_H (200 MHz, $CDCl_3$) 0.83 (q, 2H, *J* 5.3 Hz, CH_2), 1.17 (q, 2H, *J* 5.4 Hz, CH_2), 1.59–2.30 (m, 1H, CH), 2.60 (s, 3H, SCH_3), 6.72 (s, 2H, CH), 7.16–7.26 (m, 2H, ArH), 7.34–7.44 (m, 2H, ArH) (Found: C, 67.82; H, 5.06; N, 4.87. $C_{17}H_{14}ClNS$ requires C, 68.28; H, 4.91; N, 4.68%).

4-(4-Chlorophenyl)-2-ethyl-6-(methylthio)benzonitrile 2d. Yield 54%; mp 108 °C; ν_{max}/cm^{-1} 2229 (CN); *m*/*z* (EI) 287 (M^+, 100%), 283 (11), 204 (46.7); δ_H (200 MHz, $CDCl_3$) 1.22 (t, 3H, *J* 6.3 Hz, CH_3), 2.56 (s, 3H, SCH_3), 2.88 (q, 2H, *J* 5.4 Hz, CH_2), 6.90 (s, 2H, CH), 7.19–7.25 (m, 2H, ArH), 7.36–7.43 (m, 2H, ArH) (Found: C, 67.12; H, 4.82; N, 5.03. $C_{16}H_{14}ClNS$ requires C, 66.95; H, 4.91; N, 4.98%).

[4,6-Bis(4-fluorophenyl)pyran-2-ylidene]acetonitrile 3. Yield 50%; mp 149 °C; ν_{max}/cm^{-1} 2229 (CN); *m*/*z* (EI) 307 (M^+, 92%), 306 (100), 280 (46.7); δ_H (200 MHz, $CDCl_3$) 6.45 (s, 1H, CH), 6.90 (s, 1H, CH), 7.30 (s, 1H, CH), 7.52 (d, 2H, *J* 8.0 Hz, ArH), 7.58 (d, 2H, *J* 8.1 Hz, ArH), 7.72 (d, 2H, *J* 8.0 Hz, ArH), 7.86 (d, 2H, *J* 8.2 Hz, ArH) (Found: C, 74.35; H, 3.46; N, 4.25. $C_{19}H_{11}F_2NO$ requires C, 74.26; H, 3.60; N, 4.56%).

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Table 1 Physical and spectral data of compounds **5a–o**

Compd.	Yield (%)	Mp (θ/°C)[a]	ν_{max}[b]/cm^{-1}	δ_H, J/Hz[c]	m/z (%)
5a	69	>260	1689, 2000	3.42 (t, 4H, *J* 6.2, NCH_2), 4.07 (t, 4H, *J* 6.0, NCH_2), 6.42 (s, 1H, CH), 6.85–6.95 (m, 5H, ArH), 7.22–7.36 (m, 2H, ArH), 7.59–7.71 (m, 2H, ArH)	376 ($M^+ + 1$, 100), 375 (M^+, 10.2)
5b	70	195	1693, 2206	3.27 (t, 4H, *J* 6.2, NCH_2), 3.89 (s, 3H, OCH_3), 4.06 (t, 4H, *J* 6.4, NCH_2), 6.44 (s, 1H, CH), 6.89–6.95 (m, 4H, ArH), 7.17–7.26 (m, 2H, ArH), 7.79–7.87 (m, 2H, ArH)	405 (M^+, 61.2), 404 (57.5), 162 (100)
5c	71	220	1679, 2204	3.82 (t, 4H, *J* 6.3, NCH_2), 4.05 (t, 4H, *J* 6.2, NCH_2), 6.43 (s, 1H, CH), 6.67–6.73 (m, 2H, py), 7.14 (d, 1H, *J* 7.9, py), 7.21 (d, 1H, *J* 8.2, py), 7.26–7.35 (m, 2H, ArH), 7.79–7.87 (m, 2H, ArH)	377 ($M^+ + 1$, 100), 376 (M^+, 57.5)
5d	56	212	1701, 2206	2.82 (t, 4H, *J* 5.8, NCH_2), 3.88 (t, 4H, *J* 5.9, NCH_2), 4.19 (m, 1H, CH), 6.32 (s, 1H, CH), 7.16–7.35 (m, 9H, ArH), 7.74–7.87 (m, 4H, ArH)	500 ($M^+ + 1$, 68.6), 499 (M^+, 100)
5e	72	>260	1703, 2206	3.42 (t, 4H, *J* 6.0, NCH_2), 4.07 (t, 4H, *J* 6.2, NCH_2), 6.43 (s, 1H, CH), 6.84–6.98 (m, 3H, ArH), 7.13–7.35 (m, 3H, ArH), 7.80–7.87 (m, 2H, ArH)	393 (M^+, 93.8), 332 (12.5)
5f	62	200	1689, 2202	2.72 (t, 4H, *J* 6.0, NCH_2), 3.86 (t, 4H, *J* 6.4, NCH_2), 4.29 (m, 1H, CH), 6.94 (s, 1H, CH), 7.24–7.42 (m, 12H, ArH)	518 ($M^+ + 1$, 81.6), 517 (M^+, 88.6)
5g	89	220	1695, 2213	3.42 (t, 4H, *J* 6.2, NCH_2), 4.07 (t, 4H, *J* 6.0, NCH_2), 6.46 (s, 1H, CH), 6.96 (d, 2H, *J* 7.4, ArH), 7.27–7.31 (m, 3H, ArH), 7.45 (d, 2H, *J* 8.2, ArH), 7.76 (d, 2H, *J* 8.0, ArH)	391 (M^+, 95.2), 375 (5.9)
5h	84	220	1684, 2210	2.64 (t, 4H, *J* 6.0, NCH_2), 3.88 (t, 4H, *J* 6.3, NCH_2), 4.30 (s, 1H, CH), 6.57 (s, 1H, CH), 7.32–7.40 (m, 6H, ArH), 7.67–7.81 (m, 6H, ArH)	520 (M^+, 93.6), 446 (12.3)
5i	82	170	1695, 2215	3.78 (t, 4H, *J* 6.2, NCH_2), 3.90 (s, 3H, OCH_3), 4.07 (t, 4H, *J* 6.4, NCH_2), 6.47 (s, 1H, CH), 6.89–6.95 (m, 4H, ArH), 7.44–7.51 (m, 2H, ArH), 7.74–7.84 (m, 2H, ArH)	421 (M^+, 100), 277 (10.9)
5j	89	>260	1685, 2202	3.82 (t, 4H, *J* 6.3, NCH_2), 4.07 (t, 4H, *J* 6.2, NCH_2), 6.47 (s, 1H, CH), 6.62–6.76 (m, 2H, py), 7.18 (d, 1H, *J* 7.9, py), 7.27 (d, 1H, *J* 8.0, py), 7.29–7.35 (m, 2H, ArH), 7.59–7.77 (m, 2H, ArH)	393 ($M^+ + 1$, 51.5), 392 (M^+, 83.1)
5k	68	260	1699, 2218	3.43 (t, 4H, *J* 6.4, NCH_2), 4.05 (t, 4H, *J* 6.6, NCH_2), 4.19 (s, 1H, CH), 6.60 (s, 1H, CH), 6.92 (d, 2H, *J* 8.8, ArH), 6.98 (d, 2H, *J* 9.0, ArH), 7.35–7.53 (m, 5H, ArH), 7.63–7.69 (m, 4H, ArH)	516 (M^+, 58.6), 460 (28.6)
5l	59	210	1681, 2208	2.64 (t, 4H, *J* 6.2, NCH_2), 3.58 (s, 2H, CH_2), 3.88 (t, 4H, *J* 6.4, NCH_2), 6.40 (s, 1H, CH), 7.28–7.42 (m, 5H, ArH), 7.61–7.72 (m, 4H, ArH)	406 ($M^+ + 1$, 100), 405 (M^+, 68.9)
5m	70	230	1687, 2216	3.43 (t, 4H, *J* 6.2, NCH_2), 4.06 (t, 4H, *J* 6.0, NCH_2), 6.48 (s, 1H, CH), 6.94 (d, 2H, *J* 8.0, ArH), 7.21–7.35 (m, 3H, ArH), 7.53–7.90 (m, 2H, ArH), 7.91 (s, 1H, ArH)	426 (M^+, 50.4), 425 (33.8)
5n	74	210	1705, 2205	3.40 (t, 4H, *J* 6.1, NCH_2), 3.87 (s, 3H, OCH_3), 4.06 (t, 4H, *J* 6.2, NCH_2), 6.66 (s, 1H, CH), 7.27–7.35 (m, 3H, ArH), 7.46–7.92 (m, 5H, ArH)	393 (M^+, 86.4), 307 (48.3)
5o	62	178	1708, 2208	2.56 (t, 4H, *J* 6.0, NCH_2), 3.87 (t, 4H, *J* 6.3, NCH_2), 4.26 (s, 1H, CH), 6.36 (d, 2H, *J* 7.8, CH, Furyl), 6.77 (d, 1H, *J* 7.9, Furyl), 6.88–7.12 (m, 1H, Furyl), 7.32–7.40 (m, 4H, ArH), 7.67–7.81 (m, 4H, ArH)	474 ($M^+ + 1$, 50), 473 (M^+, 39.3), 461 (20.2)

[a] Uncorrected. [b] From KBr discs. [c] From $CHCl_3$.

General procedure for the synthesis of 5a–o

A mixture of a 6-aryl-3-cyano-4-methylthio-2*H*-pyran-2-one **1** (10 mmol) and *N*-substituted piperazine **4** (15 mmol) in methanol was refluxed for 6 h on a boiling water-bath. After completion of the reaction, solvent was distilled off under reduced pressure and the product obtained was filtered off and crystallized from ethanol. Characterization data for all the synthesized compounds are listed in Table 1.

General procedure for the synthesis of 6a–v

A mixture of a 6-aryl-3-cyano-4-(*N*′-substituted piperazino)-2*H*-pyran-2-one **5** (10 mmol), ketone $RCOCH_3$ (15 mmol) and potassium hydroxide (15 mmol) in dry DMF was stirred at room temperature under a nitrogen blanket for 30 h. The reaction mixture was then poured into ice–water, vigorously stirred for 30 min, and thereafter acidified with 10% HCl. The precipitate obtained was filtered off, washed with water, and purified

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Table 2 Physical and spectral data of compounds **6a**–**v**

Compd.	Yield (%)	Mp (θ/°C)[a]	ν_{max}[b]/cm^{-1}	δ_H, J/Hz[c]	m/z (%)
6a	48	145	2210	2.58 (s, 3H, CH_3), 2.64 (t, 4H, J 6.2, NCH_2), 3.41 (t, 4H, J 6.1, NCH_2), 6.86–7.00 (m, 2H, CH), 7.11–7.19 (m, 5H, ArH), 7.51–7.57 (m, 4H, ArH)	371 (M^+, 100), 340 (10.8)
6b	56	147	2218	2.57 (s, 3H, CH_3), 3.30 (t, 4H, J 5.8, NCH_2), 3.46 (t, 4H, J 6.0, NCH_2), 3.89 (s, 3H, OCH_3), 6.87–7.02 (m, 2H, CH), 7.10–7.19 (m, 4H, ArH), 7.50–7.57 (m, 4H, ArH)	401 (M^+, 100), 238 (38.5)
6c	58	158	2216	0.75–0.84 (m, 4H, CH_2), 1.18–2.26 (m, 1H, CH), 3.26 (t, 4H, J 5.7, NCH_2), 3.39 (t, 4H, J 6.2, NCH_2), 3.82 (s, 3H, OCH_3), 6.87–7.02 (m, 2H, CH), 7.03–7.11 (m, 4H, ArH), 7.29–7.46 (m, 4H, ArH)	427 (M^+, 80.2), 391 (42)
6d	64	190	2218	0.78–0.82 (m, 4H, CH_2), 1.27–1.36 (m, 1H, CH), 3.31 (t, 4H, J 6.4, NCH_2), 3.94 (t, 4H, J 6.0, NCH_2), 6.43–6.88 (m, 2H, CH), 6.99–7.03 (m, 2H, py), 7.14 (d, 1H, J 7.8, py), 7.23 (d, 1H, J 8.0, py), 7.26–7.35 (m, 2H, ArH), 7.61–7.81 (m, 2H, ArH)	398 (M^+, 51.1), 167 (39)
6e	60	140	2214	2.53 (s, 3H, CH_3), 2.61 (t, 4H, J 5.8, NCH_2), 3.25 (t, 4H, J 6.4, NCH_2), 4.30 (s, 1H, CH), 6.95 (s, 1H, CH), 7.03 (s, 1H, CH), 7.09–7.54 (m, 13H, ArH)	495 (M^+, 50), 467 (10.2)
6f	52	148	2220	1.25 (t, 3H, CH_3), 2.07–2.54 (m, 2H, CH_2), 3.38 (t, 4H, J 6.4, NCH_2), 3.88 (t, 4H, J 6.0, NCH_2), 6.52–6.73 (m, 2H, CH), 6.99–7.11 (m, 2H, py), 7.24 (d, 1H, J 7.9, py), 7.34 (d, 1H, J 8.0, py), 7.35–7.50 (m, 2H, ArH), 7.61–7.81 (m, 2H, ArH)	387 (M^+ + 1, 100), 386 (M^+, 55.3)
6g	65	140	2200	2.59 (s, 3H, CH_3), 3.40 (t, 4H, J 6.1, NCH_2), 4.06 (t, 4H, J 6.4, NCH_2), 6.42 (s, 2H, CH), 6.96 (d, 2H, J 7.4, ArH), 7.27–7.33 (m, 3H, ArH), 7.46 (d, 2H, J 7.8, ArH), 7.76 (d, 2H, J 8.0, ArH)	387 (M^+, 92.2), 320 (7.6)
6h	53	160	2205	2.53 (s, 3H, CH_3), 2.72 (t, 4H, J 6.1, NCH_2), 3.24 (t, 4H, J 6.2, NCH_2), 4.30 (s, 1H, CH), 6.86 (s, 1H, CH), 6.95 (s, 1H, CH), 7.16–7.4 (m, 13H, ArH)	512 (M^+, 50.8), 460 (10.8)
6i	56	176	2210	2.47 (s, 3H, CH_3), 2.53 (t, 4H, J 6.2, NCH_2), 3.44 (t, 4H, J 6.0, NCH_2), 4.24 (s, 1H, CH), 6.57 (s, 2H, CH), 6.87–6.98 (m, 6H, ArH), 7.30–7.42 (m, 6H, ArH)	513 (M^+, 88.8), 310 (31)
6j	68	170	2212	2.55 (s, 3H, CH_3), 3.32 (t, 4H, J 5.9, NCH_2), 3.44 (t, 4H, J 6.1, NCH_2), 3.89 (s, 3H, OCH_3), 6.88–7.02 (m, 2H, CH), 7.10–7.19 (m, 4H, ArH), 7.35–7.48 (m, 4H, ArH)	417 (M^+, 100), 402 (20.2)
6k	67	168	2214	2.58 (s, 3H, CH_3), 3.35 (t, 4H, J 6.2, NCH_2), 3.78 (t, 4H, J 6.1, NCH_2), 6.64–6.73 (m, 2H, CH), 6.99–7.26 (m, 2H, py), 7.34 (d, 1H, J 7.8, py), 7.44 (d, 1H, J 8.0, py), 7.47–7.58 (m, 2H, ArH), 7.63–7.81 (m, 2H, ArH)	388 (M^+, 33.3), 282 (18.7)
6l	39	142	2232	2.07–2.14 (m, 4H, CH_2), 2.34 (t, 4H, J 5.8, NCH_2), 3.22 (t, 4H, J 6.0, NCH_2), 3.83 (s, 3H, OCH_3), 6.44 (s, 2H, CH), 6.74–6.97 (m, 4H, ArH), 7.10–7.19 (m, 4H, ArH), 7.35–7.48 (m, 5H, ArH)	508 (M^+ + 1, 80), 507 (M^+, 74.2)
6m	36	oil	2228	0.68 (t, 3H, J 6.2, CH_3), 1.10–1.28 (m, 4H, CH_2), 1.30–1.40 (m, 4H, CH_2), 2.46 (t, 4H, J 6.2, NCH_2), 3.08 (t, 4H, J 6.0, NCH_2), 4.22 (s, 1H, CH), 6.57 (s, 2H, CH), 7.07–7.18 (m, 6H, ArH), 7.25–7.34 (m, 6H, ArH)	570 (M^+ + 1, 90), 569 (M^+, 62), 535 (70.5)
6n	40	98	2214	2.14–2.27 (m, 4H, CH_2), 2.37 (t, 4H, J 5.9, NCH_2), 3.13 (t, 4H, J 6.1, NCH_2), 4.30 (s, 1H, CH), 6.44 (s, 2H, CH), 6.85–6.98 (m, 4H, ArH), 7.16–7.23 (m, 8H, ArH), 7.30–7.40 (m, 5H, ArH)	604 (M^+ + 1, 50), 603 (M^+, 22.2)
6o	55	178	2216	0.75–0.84 (m, 4H, CH_2), 2.26–2.33 (m, 1H, CH), 3.43 (t, 4H, J 5.9, NCH_2), 3.81 (t, 4H, J 6.2, NCH_2), 3.89 (s, 3H, OCH_3), 6.87–6.99 (m, 2H, CH), 7.03–7.11 (m, 4H, ArH), 7.29–7.44 (m, 4H, ArH)	443 (M^+, 100), 279 (26.5)
6p	54	159	2214	0.75–0.83 (m, 4H, CH_2), 2.24–2.67 (m, 1H, CH), 3.34 (t, 4H, J 5.9, NCH_2), 3.48 (t, 4H, J 6.0, NCH_2), 3.67 (s, 2H, NCH_2Ph), 6.88–7.02 (m, 2H, CH), 7.06–7.19 (m, 4H, ArH), 7.29–7.46 (m, 5H, ArH)	427 (M^+, 88.2), 401 (33.5)
6q	49	152	2222	0.79–1.12 (m, 4H, CH_2), 2.29–2.36 (m, 1H, CH), 3.36 (t, 4H, J 6.4, NCH_2), 3.79 (t, 4H, J 6.2, NCH_2), 6.64–6.73 (m, 2H, CH), 6.99–7.26 (m, 2H, py), 7.36 (d, 1H, J 7.9, py), 7.43 (d, 1H, J 8.0, py), 7.47–7.58 (m, 2H, ArH), 7.71–7.85 (m, 2H, ArH)	415 (M^+ + 1, 90), 414 (M^+, 58)
6r	50	126	2214	0.76–1.18 (m, 4H, CH_2), 2.25–2.33 (m, 1H, CH), 2.60 (t, 4H, J 6.2, NCH_2), 3.25 (t, 4H, J 6.0, NCH_2), 4.31 (s, 1H, CH), 6.57 (s, 2H, CH), 6.89–6.95 (m, 6H, ArH), 7.26–7.39 (m, 6H, ArH)	540 (M^+ + 1, 60), 539 (M^+, 38.8)
6s	63	140	2218	2.53 (s, 3H, CH_3), 3.42 (t, 4H, J 6.0, NCH_2), 4.01 (t, 4H, J 6.2, NCH_2), 6.42 (s, 2H, CH), 6.86–7.01 (m, 3H, ArH), 7.29–7.41 (m, 5H, ArH)	422 (M^+, 98.2), 421 (100)
6t	58	169	2220	2.50 (s, 3H, CH_3), 2.60 (t, 4H, J 6.3, NCH_2), 3.24 (t, 4H, J 6.4, NCH_2), 4.21 (s, 1H, CH), 6.52 (s, 2H, CH), 6.60–6.75 (m, 4H, ArH), 7.03–7.17 (m, 4H, ArH), 7.26–7.36 (m, 1H, Furyl), 7.41 (d, 1H, J 8.0, Furyl), 7.49 (d, 1H, J 7.9, Furyl)	469 (M^+, 73.1), 266 (69.5)
6u	48	182	2208	0.79–1.13 (m, 4H, CH_2), 1.80–2.33 (m, 1H, CH), 2.60 (t, 4H, J 6.2, NCH_2), 3.24 (t, 4H, J 6.3, NCH_2), 4.31 (s, 1H, CH), 6.52 (s, 2H, CH), 6.71–6.94 (m, 4H, ArH), 6.99–7.09 (m, 4H, ArH), 7.27–7.34 (m, 1 H, Furyl), 7.39 (d, 1H, J 7.8, Furyl), 7.49 (d, 1H, J 7.9, Furyl)	496 (M^+ + 1, 100), 495 (M^+, 52.8)
6v	53	150	2210	2.61 (s, 3H, CH_3), 3.31 (t, 4H, J 5.8, NCH_2), 4.08 (t, 4H, J 6.1, NCH_2), 7.04 (s, 1H, CH), 7.16 (s, 1H, CH), 7.36 (s, 1H, ArH), 7.85–7.90 (m, 4H, ArH), 7.92 (s, 1H, ArH), 8.53 (d, 2H, J 8.4, ArH), 8.61 (s, 1H, ArH)	423 (M^+ + 1, 100), 422 (M^+, 50.6)

[a] Uncorrected. [b] From KBr discs. [c] From $CHCl_3$.

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Table 3 Elemental analyses of compounds **5** and **6**

Compound (Formula)	Found (%) (Required) C	H	N
5a ($C_{22}H_{18}FN_3O_2$)	70.64 (70.39)	4.59 (4.83)	11.34 (11.19)
5b ($C_{23}H_{20}FN_3O_3$)	68.04 (68.12)	4.78 (4.97)	10.59 (10.36)
5c ($C_{21}H_{17}FN_4O_2$)	67.35 (67.07)	4.75 (4.55)	14.78 (14.90)
5d ($C_{29}H_{23}ClFN_3O_2$)	69.39 (69.66)	4.75 (4.63)	8.29 (8.40)
5e ($C_{22}H_{17}F_2N_3O_2$)	66.95 (67.16)	4.63 (4.35)	10.39 (10.68)
5f ($C_{29}H_{22}ClF_2N_3O_2$)	67.39 (67.25)	4.39 (4.28)	8.42 (8.11)
5g ($C_{22}H_{18}ClN_3O_2$)	67.67 (67.48)	4.59 (4.63)	10.59 (10.62)
5h ($C_{29}H_{22}ClF_2N_3O_2$)	66.56 (66.97)	4.59 (4.26)	7.69 (8.08)
5i ($C_{23}H_{20}ClN_3O_3$)	65.66 (65.61)	4.92 (4.78)	9.68 (9.98)
5j ($C_{21}H_{17}ClN_4O_2$)	64.13 (64.33)	4.55 (4.37)	13.98 (14.29)
5k ($C_{29}H_{23}Cl_2N_3O_2$)	67.12 (67.45)	4.25 (4.48)	8.29 (8.13)
5l ($C_{23}H_{20}ClN_3O_2$)	68.04 (68.20)	4.92 (4.97)	10.58 (10.37)
5m ($C_{22}H_{17}Cl_2N_3O_2$)	62.12 (61.98)	4.35 (4.02)	9.98 (9.86)
5n ($C_{22}H_{20}FN_3O_3$)	67.22 (67.16)	5.35 (5.12)	10.39 (10.68)
5o ($C_{27}H_{21}F_2N_3O_3$)	68.34 (68.55)	4.89 (5.11)	8.59 (8.88)
6a ($C_{24}H_{22}FN_3$)	77.41 (77.60)	5.58 (5.97)	11.65 (11.31)
6b ($C_{25}H_{24}FN_3O$)	74.51 (74.87)	5.98 (6.03)	10.80 (10.67)
6c ($C_{27}H_{26}FN_3O$)	76.11 (75.94)	5.98 (6.13)	10.05 (9.84)
6d ($C_{25}H_{23}FN_4$)	75.75 (75.43)	5.55 (5.82)	14.28 (14.07)
6e ($C_{31}H_{27}ClFN_3$)	74.89 (75.06)	5.75 (5.48)	8.29 (8.47)
6f ($C_{24}H_{23}FN_4$)	74.53 (74.67)	6.13 (6.00)	14.76 (14.51)
6g ($C_{24}H_{22}ClN_3$)	73.99 (74.30)	5.76 (5.71)	10.65 (10.83)
6h ($C_{31}H_{27}Cl_2N_3$)	72.38 (72.65)	4.93 (5.31)	8.42 (8.20)
6i ($C_{31}H_{26}ClF_2N_3$)	72.48 (72.57)	5.28 (5.10)	8.59 (8.19)
6j ($C_{25}H_{24}ClN_3O$)	71.87 (72.00)	5.74 (5.80)	9.87 (10.07)
6k ($C_{23}H_{21}ClN_4$)	71.53 (71.19)	5.13 (5.45)	14.76 (14.44)
6l ($C_{32}H_{30}ClN_3O$)	75.87 (75.80)	5.74 (5.96)	8.87 (8.28)
6m ($C_{35}H_{34}ClF_2N_3$)	73.48 (73.87)	6.28 (6.02)	7.59 (7.38)
6n ($C_{38}H_{32}ClF_2N_3$)	75.87 (75.68)	5.74 (5.34)	6.87 (6.96)
6o ($C_{27}H_{26}ClN_3O$)	73.51 (73.19)	5.98 (5.91)	9.05 (9.48)
6p ($C_{27}H_{26}ClN_3$)	76.11 (76.40)	5.98 (6.07)	10.05 (9.80)
6q ($C_{25}H_{23}ClN_4$)	75.53 (75.24)	5.33 (5.60)	13.96 (13.53)
6r ($C_{33}H_{28}ClF_2N_3$)	73.98 (73.53)	5.48 (5.23)	8.09 (7.79)
6s ($C_{24}H_{21}Cl_2N_3$)	68.39 (68.25)	5.36 (5.01)	9.63 (9.95)
6t ($C_{29}H_{25}F_2N_3O$)	73.98 (74.26)	5.28 (5.37)	7.59 (7.38)
6u ($C_{31}H_{27}F_2N_3O$)	74.98 (75.21)	5.90 (5.49)	8.09 (8.48)
6v ($C_{24}H_{22}N_8$)	68.14 (68.23)	5.36 (5.25)	26.28 (26.52)

on a silica gel column, using chloroform–hexane (1 : 1) as eluent. Characterization data for all the synthesized compounds are listed in Table 2. Elemental analyses of compounds **5** and **6** are listed in Table 3.

X-Ray crystallographic data ‡

Crystal data for 5h. $C_{29}H_{22}ClF_2N_3O_2$, $M = 517.95$, monoclinic, $C2/c$, $a = 44.292(4)$ $b = 7.662(1)$, $c = 14.949(1)$ Å, $\beta = 92.71(0)°$, $V = 5067.5(9)$ Å^3, $Z = 8$, $D_c = 1.358$ g cm^{-1}, μ(Mo-Kα) = 0.198 mm^{-1}, $F(000) = 2144.0$, yellowish plate crystal, size 0.375 × 0.275 × 0.075 mm, 5759 reflections measured ($R_{int} = 0.033$), 4445 unique, $R_w = 0.124$ for all data, conventional $R = 0.054$ [$(\Delta/\sigma)_{max} = 0.000$] on F-values of 2219 reflections with $I > 2\sigma(I)$, $S = 1.006$ for all data and 334 parameters. Final difference map between 0.172 and −0.297 e Å^{-3}.

Crystal data for 6q. $C_{25}H_{23}ClN_4$, $M = 414.92$, triclinic, $P(-1)$, $a = 8.452(1)$, $b = 12.398(1)$, $c = 21.137(1)$ Å, $\alpha = 75.02(1)$, $\beta = 83.19(1)$, $\gamma = 81.70(1)°$, $V = 2109.6(4)$ Å^3, $Z = 4$, $D_c = 1.307$ g cm^{-1}, μ(Mo-Kα) = 0.201 mm^{-1}, $F(000) = 872.0$, colourless block crystal, size 0.425 × 0.352 × 0.200 mm, 8900 reflections measured ($R_{int} = 0.028$), 7258 unique, $R_w = 0.143$ for all data, conventional $R = 0.055$ [$(\Delta/\sigma)_{max} = 0.000$] on F-values of 5254 reflections with $I > 2\sigma(I)$, $S = 0.962$ for all data and 542 parameters. Final difference map between 0.62 and −0.59 e Å^{-3}. Unit-cell determination and intensity-data collection ($2\theta = 50°$) for both compounds were performed on a Bruker P4 diffractometer at 293(2) K. Structure solutions by direct methods and refinements by full-matrix least-squares methods on F^2. Programs: XSCANS[26] (data collection and data processing), SHELXTL-NT[27] (structure determination and refinements) and NRCVAX[28] (molecular graphics).

The ORTEP[28] diagrams of **5h** (Fig. 1) and **6q** (Fig. 3) and crystal packing (PLUTO[28]) of **5h** (Fig. 2) are shown.

‡ CCDC reference numbers 164198 and 164199. See http://www.rsc.org/suppdata/p1/b0/b009725j/ for crystallographic files in .cif or other electronic format.

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