A Convenient Regioselective Synthesis of 6-Amino-2-oxo-3,5-pyridinedicarbonitriles

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Reaction of cyanoacetohydrazones **3a,b** with a variety of arylidenemalononitriles **5a – c** under the effect of piperidine basic catalysis afforded exclusively the corresponding 6-amino-1,2-dihydro-1,4-disubstituted-2-oxo-3,5-pyridinedicarbonitriles **6a – f** in high regioselectivity. A chemical confirmation for the proposed structure was achieved through the reaction of ylidenes **8** with malononitrile under basic conditions, which yielded the corresponding **6** accompanied with **3**. Refluxing **3b** in acetic anhydride gave 2-acetyl-3-cyanomethyl-4,5-dihydro-2*H*-benz[*g*]indazole (**10**) as the only isolable product. Single crystal X-ray diffraction of **6e** and **10** add conclusive support for the established structures.

Key words: Arylidenemalononitriles, 3,5-Pyridinedicarbonitriles, Cyanoacetohydrazones, 2*H*-Benz[*g*]indazoles, Michael Reaction

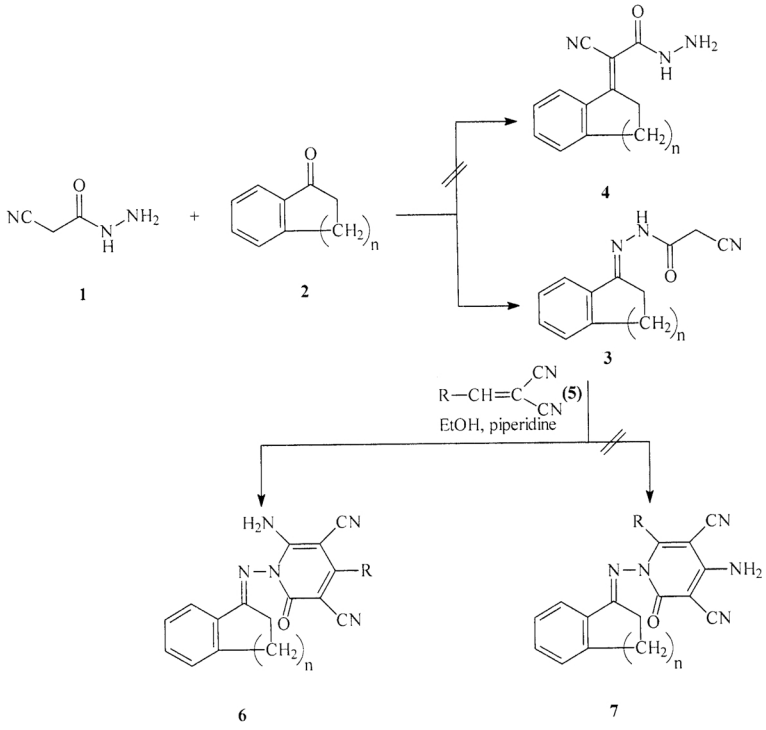
Introduction

Many publications report the biological properties of 3,5- pyridinedicarbonitriles as being antihypertensive [1,2], antihistaminic [3], anticancer [4], in addition to antibacterial [5 – 7] or antifungal [6 – 8]. In the light of all the previous reports, it is intended in the present work to investigate the synthesis of novel 3,5-pyridinedicarbonitrile derivatives *via* a facile synthetic approach utilizing easily prepared accessible chemical materials. The regioselectivity of the reactions was also investigated.

Results and Discussion

Reaction of cyanoacetohydrazide (**1**) with cycloalkanones **2** (namely, 1-indanone **2a** and α-tetralone **2b**) in refluxing ethanol in either presence or absence of a catalytic amount of piperidine afforded the corresponding hydrazones **3a,b**. The structure of **3** was established through spectroscopic (IR, ^{1}H NMR, mass) and elemental analyses data. The appearance of a singlet signal in ^{1}H NMR spectra at $\delta = 3.90$, 3.94 in case of **3a** and **3b** respectively, assignable for the active methylene function, excludes the formation of the ylidene structure **4**.

Reaction of **3a,b** with arylidenemalononitriles **5a – c** in refluxing ethanol in the presence of a catalytic amount of piperidine afforded colourless to pale yellow products, the structure of which was established to be 6-amino-2-oxo-3,5-pyridinedicarbonitriles **6a – f** or their isomeric forms **7a – f** based on spectroscopic data and elemental analyses (Scheme 1). The IR spectra reveal the nitrile and carbonyl stretching vibration bands at $\nu = 2217 - 2211$, $1675 - 1654$ cm^{-1} respectively. In addition, ^{1}H NMR spectra exhibit the amino singlet signal at $\delta = 8.16 - 8.37$. The isolated products were established to be **6** rather than **7** based on the independent synthesis of **6c,f** as representative examples through the reaction of the corresponding ylidenes **8a,b** with malononitrile in the presence of piperidine as a basic catalyst. The reaction is smoothly proceeded affording a mixture of **6** and **3**. The two compounds were separated by chromatographically using silica gel TLC. The isolation of **3** could be attributed to the retro-Aldol pathway taking place under the applied reaction conditions (Scheme 2). ^{13}C NMR (decoupled & APT) spectra of **6e** add a conclusive support for the proposed structure, which reveal the quaternary pyridine C-5 and C-3 at $\delta = 75.07$, 87.07 respectively; in addition to the nitrile carbons at $\delta = 115.34$, 116.23. Single crystal X-ray diffraction of **6e** (Fig. 1) confirms the established structure [9]. From all the above, it could be concluded that the reaction of **3** with **5** under the described reaction conditions seems to be highly



2a, **3a**; n = 1

2b, **3b**; n = 2

5a; R = Ph

5b; R = 4-ClC_6H_4

5c; R = 4-$H_3COC_6H_4$

6a; R = Ph, n = 1

6b; R = 4-ClC_6H_4, n = 1

6c; R = 4-$H_3COC_6H_4$, n = 1

6d; R = Ph, n = 2

6e; R = 4-ClC_6H_4, n = 2

6f; R = 4-$H_3COC_6H_4$, n = 2

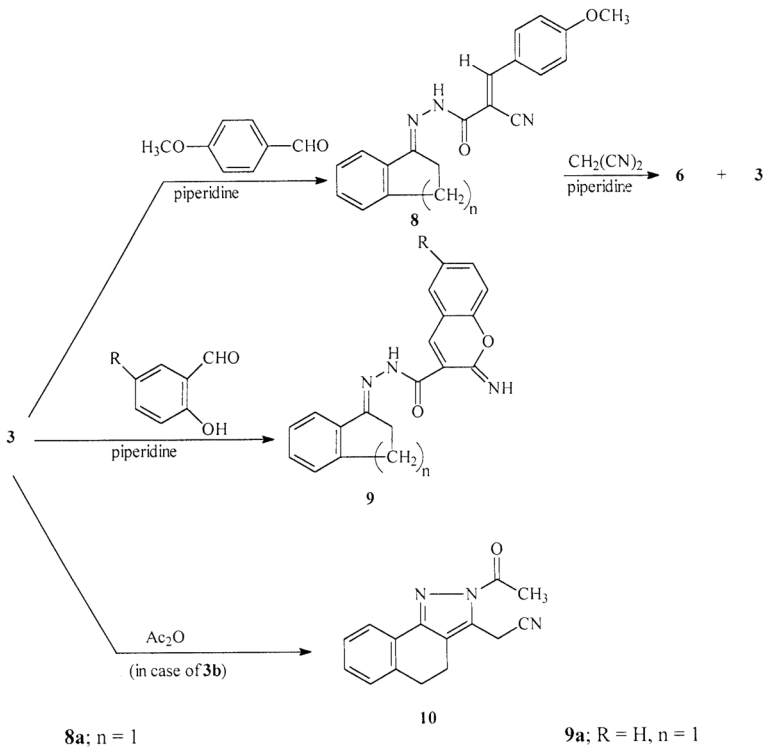
Scheme 1.

regioselective affording only one regioisomer, which structure was established to be **6**.

Formation of the ylidenes **8a,b** was achieved through the reaction of **3** with *p*-anisaldehyde in the presence of a catalytic amount of piperidine. ^{1}H NMR spectra of **8** reveal the absence of the active methylene group and exhibit the ylidene olefinic proton at $\delta = 8.41, 8.17$, in case of **8a** and **8b** respectively. The appearance of the olefinic proton signal at this chemical shift value indicates that the methine proton is located in a *trans* position to the nitrile group (*E*-form) [10, 11]. ^{13}C NMR (APT) spectrum of **8b** exhibits the olefinic quaternary carbon at $\delta = 101.82$, in addition to the nitrile and carbonyl carbons at $\delta = 116.40, 162.17$ respectively.

On the other hand, reaction of **3a,b** with salicylaldehydes afforded the corresponding 2-imino-2*H*-[1]benzopyran-3-carboxylic acid hydrazones **9a – d**. The reaction probably takes place through condensation of the aldehydic group with the active methylene function followed by nucleophilic attack of the hydroxyl group on the neighbouring nitrile residue eventually giving the corresponding **9**. The absence of the nitrile group in IR spectra of **9** confirms the cyclization process. Also, ^{1}H NMR spectra of **9a – d** reveal the benzopyran H-4 as a singlet signal at $\delta = 8.55 - 8.62$. The isolation of the benzopyran **9** from the reaction supports the intermediacy of the *E*-geometrical isomer during the reaction course. The nitrile group must be in a *trans* position to the olefinic proton in the intermediate ylidene structure, as only this geometrical isomer can easily undergo cyclization to the corresponding benzopyran **9**.

Refluxing **3b** in acetic anhydride afforded 2-acetyl-3-cyanomethyl-4,5-dihydro-2*H*-benz[*g*]indazole (**10**) as the only isolable product. The reaction presum-



8a; n = 1

8b; n = 2

9a; R = H, n = 1

9b; R = Cl, n = 1

9c; R = H, n = 2

9d; R = Cl, n = 2

Scheme 2.

ably proceeds *via* condensation of the hydrazone carbonyl with one of the cycloalkane methylene groups accompanied with acetylation of the NH function finally giving **10**. ^{1}H NMR spectrum of **10** supports the proposed structure which reveals the presence of only two adjacent methylene groups of which each appears as a triplet signal at $\delta = 2.86$, 2.99 in addition to the acetyl and cyanomethylene protons at $\delta = 2.77$, 4.19 respectively. The ^{13}C NMR (APT) spectrum of **10** exhibits just two benzindazole methylene carbons at $\delta = 16.70$, 18.85 in addition to the cyanomethylene carbon at $\delta = 28.95$. Single crystal X-ray diffraction of **10** (Fig. 2) confirms the established structure. From the X-ray data, it can be concluded that the equivalent positions of the space group P21/c are 4 positions. Therefore, the number of molecules per unit cell are 8 molecules. Hence, there are two molecules of the assigned structure compound per asymmetric unit cell [9].

Experimental Section

Melting points are uncorrected and were recorded on an Electrothermal 9100 melting point apparatus. IR spectra (KBr) were recorded on a JASCO FT/IR 300E spectrophotometer. ^{1}H NMR spectra were recorded on a Varian MERCURY 300 MHz spectrometer. ^{13}C NMR spectra were recorded on a Varian MERCURY 300 (75 MHz) spectrometer. Mass spectra were recorded on a Finnigan SSQ 7000 (EI 70 eV) spectrometer. The starting compounds **5a–c** [12,13] were prepared according to the reported procedures.

Reaction of cyanoacetohydrazide with **2a**, **b**

A mixture of equimolar amounts of cyanoacetohydrazide (**1**) and the appropriate **2** (10 mmol) in absolute ethanol (20 ml) (in either presence or absence of piperidine "3–5 drops" as a basic catalyst) was boiled under reflux for the appropriate time. The solid separated upon storing the reaction mixture to cool at room temperature overnight, was collected and crystallized from a suitable solvent affording the corresponding **3a,b**.

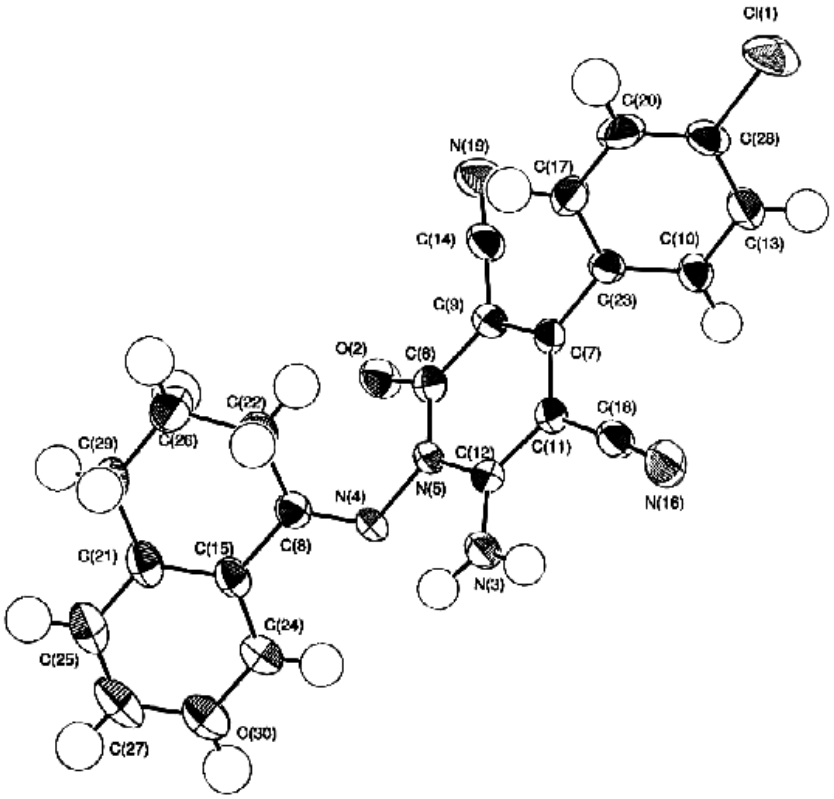


Fig. 1. Single crystal X-ray diffraction of **6e**.

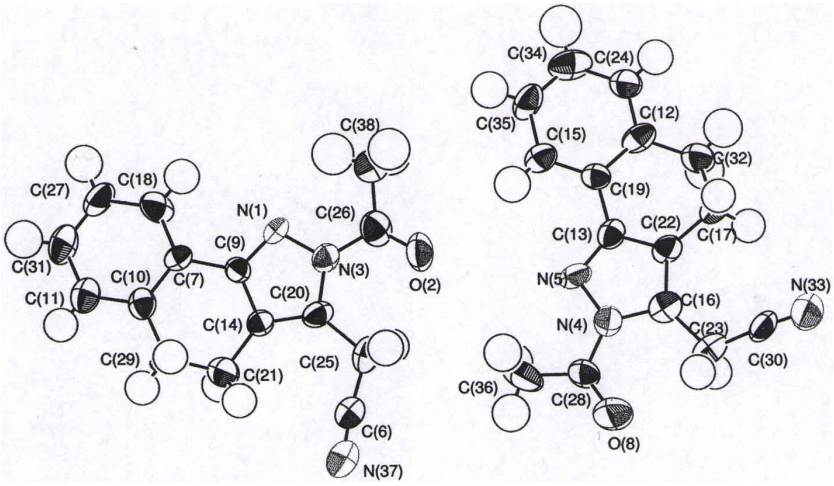


Fig. 2, Single crystal X-ray diffraction of **10**.

*2'-(2,3-Dihydroindene-1(1H)-ylidene)-2-cyanoacetic acid hydrazide (***3a***)*

Reaction time 5, 25 h (in presence and absence of piperidine, respectively), colourless crystals from ethanol, M.p. 188 – 190 °C, yield 47, 80% (in presence and absence of piperidine, respectively). – IR: $\nu = 3185$ (NH), 2258 (C≡N), 1691 (C=O), 1639, 1484 cm^{-1} (C=N, C=C).-^{1}H NMR ($CDCl_3$): $\delta = 2.78$ (t, $J = 6.3$ Hz, 2H, CH_2-CH_2), 3.14 (t, $J = 6.6$ Hz, 2H, CH_2-CH_2), 3.90 (s, 2H, CH_2-CN), 7.20 – 7.40 (m, 3H, arom. H), 7.66 (d, $J = 7.8$ Hz, 1H, arom. H), 9.35 (s, 1H, NH). – MS: m/z (%) = 213 (99) [M^+], 173

Table 1. Single crystal X-ray experimental data of compounds **6e** and **10**.

	Compd. **6e**	Compd. **10**
Chemical formula	$C_{23}H_{16}ClN_5O$	$C_{15}H_{13}N_3O$
Chemical formula weight	413.868	251.289
Exptl. crystal description	prismatic	needles
Exptl. crystal colour	colourless	yellow
Cell measurement temperature	298 K	298 K
Diffraction measurement device	Kappa CCD	Kappa CCD
Computing data collection	Kappa CCD	Kappa CCD
Computing data reduction	Denzo and Scalepak (Otwinowski & Minor, 1997)	
Diffraction reflections limit *h* min.	−12	−21
Diffraction reflections limit *h* max.	12	21
Diffraction reflections limit *k* min.	−9	−8
Diffraction reflections limit *k* max.	9	7
Diffraction reflections limit *l* min.	−15	−27
Diffraction reflections limit *l* max.	15	27
Cell formula units z	2	8
Exptl. crystal density diffraction	1.371 g/cm^3	1.340 g/cm^3
Space group	monoclinic *P*21	monoclinic *P*21/c
Unit-cell dimensions		
a/Å	10.0574 (3)	18.9485 (10)
b/Å	8.0652 (3)	7.1168 (4)
c/Å	13.1638 (4)	23.583 (2)
Cell angle		
α	90.00	90.00
β	110.079 (2)	128.429
γ	90.00	90.00
Cell volume, *V*/Å^3	1002.88 (6)	2491.3 (3)
Diffraction reflections number	3230	7559
Diffraction reflections theta max.	25.38	24.38
Diffraction reflections theta min.	3.02	3.07
Diffraction reflections theta full	25.38	24.38
Cell measurement reflections used	1720	3959
Cell measurement theta min.	2.910	2.910
Cell measurement theta max.	25.350	24.407
Diffraction measurement method	CCD	CCD

	Compd. **6e**	Compd. **10**
Computing cell refinement	HKL Scalepack (Otwinowski & Minor 1997)	
Diffraction reflections average R equivalents	0.028	0.053
Computing structure solution		SIR92 (Altomare *et al*., 1994)
Exptl. absorpt. coefficient mu	0.22	0.09
Exptl. crystal F 000	428	1056
Refinement statistics		
Reflections d resolution low	1.84	1.82
Reflections d resolution high	0.64	0.66
Reflections limit *h* max.	12	21
Reflections limit *h* min.	0	0
Reflections limit *k* max.	9	8
Reflections limit *k* min.	0	0
Reflections limit *l* max.	14	21
Reflections limit *l* min.	−15	−27
Refine 1s matrix type	full	full
Refine-1s-shift/su-max.	0.027	0.436
Refine-1s-shift/su-mean	0.008	0.074
Reflections number total	2010	4734
Refine-1s-R-factor-all	0.044	0.251
Refine-1s-wR-factor-all	0.076	0.281
Refine-1s-goodness-of-fit-all	0.919	4.201
Reflections number gt	1676	1821
Refine 1s R factor gt	0.035	0.137
Refine 1s wR factor gt	0.074	0.265
Refine 1s goodness of fit gt	0.906	6.335
Refine 1s number reflections	1675	1817
Refine 1s number parameters	271	343
Refine 1s number restraints	0	0
Refine 1s number constraints	16	27
Refine 1s wR factor ref.	0.074	0.265
Refine 1s goodness of fit ref.	0.906	6.341
Computing structure refinement	"Maxus (Mackay *et al*., 1999)"	
Computing molecular graphics	"Ortep (Johnson, 1976)"	

(35), 145 (42), 130 (74), 129 (100), 116 (58). $C_{12}H_{11}N_3O$ (213.23): calcd. C 67.59, H 5.20, N 19.71; found C 67.63, H 5.21, N 19.74.

*2'-(3,4-Dihydronaphthalene-1(2H)-ylidene)-2-cyanoacetic acid hydrazide (***3b***)*

Reaction time 5, 16 h (in presence and absence of piperidine, respectively), colourless crystals from ethanol, M.p. 182 – 184 °C, yield 44, 84% (in presence and absence of piperidine, respectively). – IR: $\nu = 3189$ (NH), 2264 (C≡N), 1689 (C=O), 1617, 1490 cm^{-1} (C=N, C=C). – ^{1}H NMR ($CDCl_3$): $\delta = 1.99$ (pentat, $J = 6.3$ Hz, 2H, CH_2-CH_2), 2.63 (t, $J = 6.6$ Hz, 2H, CH_2-CH_2), 2.80 (t, $J = 6.0$ Hz, 2H, CH_2-CH_2), 3.94 (s, 2H, CH_2-CN), 7.15 – 7.33 (m, 3H, arom. H), 8.01 (d, $J = 7.5$ Hz, 1H, arom. H), 9.61 (s, 1H, NH). – MS: m/z (%) = 227 (100) [M$^+$], 226 (90), 187 (74), 159 (87), 144 (83), 130 (33), 129 (70). $C_{13}H_{13}N_3O$ (227.25): calcd. C 68.70, H 5.76, N 18.49; found C 68.76, H 5.80, N 18.46.

6-Amino-1,2-dihydro-1,4-disubstituted-2-oxo-3,5-pyridinedicarbonitriles **6a – f**

Method "A": A mixture of equimolar amounts of the appropriate **3** and the corresponding **5** (10 mmol) in absolute ethanol (20 ml) containing piperidine (2 – 3 drops) was boiled under reflux for the appropriate time. The solid separated while refluxing was collected and crystallized from a suitable solvent affording the corresponding **6a – f**.

Method "B": A mixture of equimolar amounts of the appropriate **8** and malononitrile (5 mmol) in tetrahydrofuran or dioxane (20 ml) "in case of **8a** and **8b**, respectively" containing piperidine (2 – 3 drops) was boiled under reflux for the appropriate time. The reaction mixture was evaporated till dryness under reduced pressure. The residue was triturated with methanol (5 ml). So, the separated solid was collected and purified on silica gel (F 254) TLC using chloroform "in case of **8b**" or chloroform-light petroleum (60 – 80 °C) as 7:1 v/v for elution "in case of **8a**", affording the corresponding **6** and **3** (yield 34, 44% for **3a** and **3b** respectively).

*6-Amino-1,2-dihydro-1-[(2,3-dihydroindene-1(1H)-ylidene)-amino]-2-oxo-4-phenyl-3,5-pyridinedicarbonitrile (***6a***)*

Reaction time 12 h (method A), pale yellow crystals from *N*,*N*- dimethylformamide (80%), M.p. 292 – 294 °C, yield 55%. – IR: $\nu = 3440$, 3320 (NH_2), 2213 (C≡N), 1675 (C=O), 1596, 1548 cm^{-1} (C=N, C=C). – ^{1}H NMR (DMSO-d_6): $\delta = 2.87$ (t, $J = 6.3$ Hz, 2H, CH_2), 3.16 (t, $J = 6.0$ Hz, 2H, CH_2), 7.41 – 7.75 (m, 8H, arom. H), 8.04 (d, $J = 7.5$ Hz, 1H, arom. H), 8.37 (s, 2H, D_2O exchangeable NH_2). – MS:

m/z (%) = 365 (10) [M^+], 364 (20), 277 (100), 249 (3). $C_{22}H_{15}N_5O$ (365.38): calcd. C 72.31, H 4.14, N 19.17; found C 72.27, H 4.11, N 19.14.

*6-Amino-4-(4-chlorophenyl)-1,2-dihydro-1-[(2,3-dihydro-indene-1(1H)-ylidene)amino]-2-oxo-3,5-pyridinedicarbo-nitrile (***6b***)*

Reaction time 24 h (method A), pale yellow crystals from *n*-butanol, M.p. 306 – 308 °C, yield 50%. – IR: ν = 3407, 3309 (NH_2), 2215 (C≡N), 1658 (C=O), 1590, 1525 cm^{-1} (C=N, C=C). – ^{1}H NMR (DMSO- d_6): δ = 2.85 (t, J = 6.3 Hz, 2H, CH_2), 3.17 (t, J = 6.0 Hz, 2H, CH_2), 7.40 – 7.74 (m, 7H, arom. H), 8.03 (d, J = 7.5 Hz, 1H, arom. H), 8.36 (s, 2H, D_2O exchangeable NH_2). – MS: m/z (%) = 399 (45) [M^+], 398 (100), 283 (13). $C_{22}H_{14}ClN_5O$ (399.82): calcd. C 66.08, H 3.53, N 17.52; found C 66.11, H 3.54, N 17.39.

*6-Amino-1,2-dihydro-1-[(2,3-dihydroindene-1(1H)-ylidene)-amino]-4-(4-methoxyphenyl)-2-oxo-3,5-pyridinedicarbo-nitrile (***6c***)*

Reaction time 18, 12 h (method A & B respectively), pale yellow crystals from *N*,*N*-dimethylformamide-methanol as 1:10 v/v, M.p. 300 – 302 °C, yield 43, 18% (method A & B respectively). – IR: ν = 3405, 3305 (NH_2), 2211 (C≡N), 1656 (C=O), 1590, 1519 cm^{-1} (C=N, C=C). – ^{1}H NMR (DMSO- d_6): δ = 2.76 (t, J = 6.3 Hz, 2H, CH_2), 3.07 (t, J = 6.0 Hz, 2H, CH_2), 3.83 (s, 3H, OCH_3), 7.08 – 7.63 (m, 7H, arom. H), 7.94 (d, J = 7.2 Hz, 1H, arom. H), 8.19 (s, 2H, D_2O exchangeable NH_2).-MS: m/z (%) = 395 (45) [M^+], 394 (100), 279 (13). $C_{23}H_{17}N_5O_2$ (395.41): calcd. C 69.86, H 4.33, N 17.71; found C 69.97, H 4.42, N 17.79.

*6-Amino-1,2-dihydro-1-[(3,4-dihydronaphthalene-1(2H)-ylidene)amino]-2-oxo-4-phenyl-3,5-pyridinedicarbonitrile (***6d***)*

Reaction time 18 h (method A), colourless crystals from ethanol, M.p. 278 – 280 °C, yield 50%. – IR: ν = 3300, 3203 (NH_2), 2217 (C≡N), 1666 (C=O), 1635, 1583 cm^{-1} (C=N, C=C). – ^{1}H NMR (DMSO-d_6): δ = 1.91 – 2.03 (m, 2H, CH_2), 2.46 – 2.64 (m, 2H, CH_2), 2.86 - -2.95 (m, 2H, CH_2), 7.41 – 7.76 (m, 8H, arom. H), 8.30 (s, 2H, D_2O exchangeable NH_2), 8.35 (d, J = 8.1 Hz, 1H, arom. H). – MS: m/z (%) = 379 (40) [M^+], 350 (100), 263 (44), 250 (35). $C_{23}H_{17}N_5O$ (379.41): calcd. C 72.81, H 4.52, N 18.46; found C 72.97, H 4.64, N 18.36.

*6-Amino-4-(4-chlorophenyl)-1,2-dihydro-1-[(3,4-dihydro-naphthalene-1(2H)-ylidene)amino]-2-oxo-3,5-pyridine-dicarbonitrile (***6e***)*

Reaction time 16 h (method A), colourless crystals from *N*,*N*- dimethylformamide (50%), M.p. 289 – 291 °C, yield 53%. – IR: ν = 3448, 3289 (NH_2), 2215 (C≡N), 1654 (C=O), 1625, 1556 cm^{-1} (C=N, C=C). – ^{1}H NMR (DMSO-d_6): δ = 1.80 – 1.95 (m, 2H, CH_2), 2.49 – 2.55 (m, 2H, CH_2), 2.89 – 2.95 (m, 2H, CH_2), 7.33 – 7.66 (m, 7H, arom. H), 8.26 (s, 2H, D_2O exchangeable NH_2), 8.27 (d, J = 7.8 Hz, 1H, arom. H). – ^{13}C NMR (decoupled & APT) (DMSO-d_6): δ = 21.66, 28.33, 28.96 ($3CH_2$), 75.07, 87.07 (pyr. C-5, C-3 respectively), 115.34, 116.23 (C≡N), 126.02, 126.83, 128.67, 128.83, 130.00, 132.30 (arom. CH), 129.85, 133.40, 134.94, 142.26, 153.16, 154.57, 158.29 (arom. quaternary C), 178.78 (CO). – MS: m/z (%) = 413 (48) [M^+], 394 (100), 384 (86), 297 (28), 284 (30). $C_{23}H_{16}ClN_5O$ (413.85): calcd. C 66.75, H 3.90, N 16.92; found C 66.66, H 3.86, N 16.90.

*6-Amino-1,2-dihydro-1-[(3,4-dihydronaphthalene-1(2H)-yl-idene)amino]-4-(4-methoxyphenyl)-2-oxo-3,5-pyridine-dicarbonitrile (***6f***)*

Reaction time 18, 23 h (method A & B respectively), colourless crystals from *N*,*N*-dimethylformamide (80%), M.p. 269 – 271 °C, yield 54, 24%. – IR: ν = 3440, 3305 (NH_2), 2213 (C≡N), 1673 (C=O), 1625, 1604 cm^{-1} (C=N, C=C). – ^{1}H NMR (DMSO-d_6): δ = 1.82 – 1.89 (m, 2H, CH_2), 2.45 – 2.58 (m, 2H, CH_2), 2.87 – 2.93 (m, 2H, CH_2), 3.85 (s, 3H, OCH_3), 7.10 – 7.54 (m, 7H, arom. H), 8.16 (s, 2H, D_2O exchangeable NH_2), 8.27 (d, J = 7.8 Hz, 1H, arom. H). – MS: m/z (%) = 409 (63) [M^+], 380 (100), 293 (64), 280 (23). $C_{24}H_{19}N_5O_2$ (409.43): calcd. C 70.40, H 4.68, N 17.11; found C 70.26, H 4.60, N 17.23.

Reaction of **3a**,**b** *with aldehydes*

A mixture of equimolar amounts of the appropriate **3** and the corresponding aldehyde (5 mmol) in absolute ethanol (15 ml) containing piperidine (2 – 3 drops), was boiled under reflux for the appropriate time (in case of **3a** the reaction was stirred at room temperature "20 – 25 °C" in tetrahydrofuran "20 ml" instead of ethanol). The separated solid was collected and crystallized from a suitable solvent affording the corresponding **8a,b**, **9a – d**.

*2-Cyano-2'-(2,3-dihydroindene-1(1H)-ylidene)-3-(4-methoxyphenyl)-2-propenoic acid hydrazide (***8a***)*

Reaction time 3 days, pale yellow crystals from benzene, M.p. 199 – 201 °C, yield 79%. – IR: ν = 3350 (NH), 2206 (C≡N), 1679 (C=O), 1619, 1585 cm^{-1} (C=N, C=C). – ^{1}H NMR ($CDCl_3$): δ = 2.89 (t, J = 6.0 Hz, 2H, CH_2), 3.22 (t, J = 6.0 Hz, 2H, CH_2), 3.90 (s, 3H, OCH_3), 6.99 – 7.41 (m, 6H, arom. H), 8.00 (d, J = 8.1 Hz, 2H, p-subst. benzene), 8.41 (s, 1H, olefinic CH), 8.97 (s, 1H, NH). – MS: m/z (%) = 331 (31) [M^+], 330 (23), 201 (33), 187 (15), 186 (100), 158 (18). $C_{20}H_{17}N_3O_2$ (331.36): calcd. C 72.49, H 5.17, N 12.68; found C 72.55, H 5.22, N 12.73.

*2-Cyano-2'-(3,4-dihydronaphthalene-1(2H)-ylidene)-3-(4-methoxyphenyl)-2-propenoic acid hydrazide (**8b**)*

Reaction time 5 h, pale yellow crystals from benzene, M.p. 225 – 227 °C, yield 75%. – IR: $\nu = 3380$ (NH), 2202 (C≡N), 1689 (C=O), 1589, 1560 cm^{-1} (C=N, C=C). – ^{1}H NMR (DMSO-d_6): $\delta = 1.90$ (pentat, $J = 6.0$ Hz, 2H, CH_2), 2.72 – 2.82 (m, 4H, 2 CH_2), 3.91 (s, 3H, OCH_3), 7.16 – 8.14 (m, 8H, arom. H), 8.17 (s, 1H, olefinic CH), 10.80 (br. s, 1H, NH). – ^{13}C NMR (APT) (DMSO-d_6): $\delta = 20.83$, 25.29, 28.34 ($3CH_2$), 55.10 (OCH_3), 101.82 (olefinic quaternary C), 116.40 (C≡N), 108.75, 114.27, 124.39, 125.66, 127.99, 128.93, 132.03 (arom. CH), 124.18, 131.43, 139.69 (arom. quaternary C), 162.17 (CO). – MS: m/z (%) = 345 (61)[M^+], 344 (67), 201 (5), 187 (26), 186 (100), 158 (30). $C_{21}H_{19}N_3O_2$ (345.38): calcd. C 73.02, H 5.54, N 12.17; found C 72.87, H 5.46, N 12.20.

*2'-(2,3-Dihydroindene-1(1H)-ylidene)-2-imino-2H-[1]benzopyran-3-carboxylic acid hydrazide (**9a**)*

Reaction time 3 days, pale yellow crystals from toluene, M. p. 230 – 232 °C, yield 95%. – IR: $\nu = 3313$ (NH), 1683 (C=O), 1606, 1567 cm^{-1} (C=N, C=C). – ^{1}H NMR (DMSO-d_6): $\delta = 2.82$ (t, $J = 6.6$ Hz, 2H, CH_2), 3.15 (t, $J = 6.5$ Hz, 2H, CH_2), 7.24 – 7.83 (m, 7H, arom. H), 8.58 (s, 1H, benzopyran H-4), 9.14 (s, 1H, NH), 13.25 (s, 1H, NH). $C_{19}H_{15}N_3O_2$ (317.33): calcd. C 71.91, H 4.76, N 13.24; found C 71.86, H 4.72, N 13.23.

*6-Chloro-2'-(2,3-dihydroindene-1(1H)-ylidene)-2-imino-2H-[1]benzopyran-3-carboxylic acid hydrazide (**9b**)*

Reaction time 2 days, pale yellow crystals from *N*,*N*-dimethylformamide, M. p. 243 – 245 °C, yield 97%. – IR: $\nu = 3320$ (NH), 1681 (C=O), 1598, 1567 cm^{-1} (C=N, C=C). – ^{1}H NMR (DMSO-d_6): $\delta = 2.82$ (t, $J = 6.3$ Hz, 2H, CH_2), 3.15 (t, $J = 6.6$ Hz, 2H, CH_2), 7.26 – 7.97 (m, 7H, arom. H), 8.57 (s, 1H, benzopyran H-4), 9.33 (s, 1H, NH), 13.20 (s, 1H, NH). – MS: m/z (%) = 351 (44)[M^+], 205 (100), 179 (95), 145 (36). $C_{19}H_{14}ClN_3O_2$ (351.77): calcd. C 64.87, H 4.01, N 11.95; found C 64.97, H 4.10, N 11.88.

*2'-(3,4-Dihydronaphthalene-1(2H)-ylidene)-2-imino-2H-[1]benzopyran-3-carboxylic acid hydrazide (**9c**)*

Reaction time 9 h, pale yellow crystals from benzene, M.p. 227 – 229 °C, yield 91%. – IR: $\nu = 3289$ (NH), 1683 (C=O), 1602, 1571 cm^{-1} (C=N, C=C). – ^{1}H NMR (DMSO-d_6): $\delta = 1.94$ (pentat, $J = 6.6$ Hz, 2H, CH_2), 2.69 (t, $J = 6.6$ Hz, 2H, CH_2), 2.82 (t, $J = 6.6$ Hz, 2H, CH_2), 7.24 – 8.16 (m, 8H, arom. H), 8.62 (s, 1H, benzopyran H-4), 9.22 (s, 1H, NH), 13.48 (s, 1H, NH). – MS: m/z (%) = 331 (50)[M^+], 145 (100). $C_{20}H_{17}N_3O_2$ (331.36): calcd. C 72.49, H 5.17, N 12.68; found C 72.52, H 5.19, N 12.70.

*6-Chloro-2'-(3,4-dihydronaphthalene-1(2H)-ylidene)-2-imino-2H-[1]benzopyran-3-carboxylic acid hydrazide (**9d**)*

Reaction time 9 h, pale yellow crystals from toluene, M.p. 237 – 239 °C, yield 88%. – IR: $\nu = 3320$ (NH), 1679 (C=O), 1604, 1569 cm^{-1} (C=N, C=C). – ^{1}H NMR (DMSO-d_6): $\delta = 1.90$ (pentat, $J = 6.3$ Hz, 2H, CH_2), 2.63 (t, $J = 6.3$ Hz, 2H, CH_2), 2.77 (t, $J = 6.3$ Hz, 2H, CH_2), 7.19 – 8.11 (m, 7H, arom. H), 8.55 (s, 1H, benzopyran H-4), 9.31 (s, 1H, NH), 13.40 (s, 1H, NH). – MS: m/z (%) = 365 (42)[M^+], 205 (61), 179 (100), 145 (3). $C_{20}H_{16}ClN_3O_2$ (365.80): calcd. C 65.66, H 4.41, N 11.49; found C 65.54, H 4.38, N 11.55.

*2-Acetyl-3-cyanomethyl-4,5-dihydro-2H-benz[g]indazole (**10**)*

A solution of **3b** (10 mmol) in acetic anhydride (20 ml) was boiled under reflux for 1 h. Then, poured into ice-cold water (200 ml) while stirring and stored at room temperature overnight. The oily mass formed was extracted with chloroform (50 ml). The chloroform solution was evaporated till dryness under reduced pressure, the remaining material was solidified with a mixture of benzene:n-hexane as 1:5 v/v (10 ml) and crystallized from ethanol affording the corresponding **10** as yellow crystals, M.p. 171 – 172 °C, yield 20%. – IR: $\nu = 2250$ (C≡N), 1718 (C=O), 1525, 1473 cm^{-1} (C=N, C=C). – ^{1}H NMR ($CDCl_3$): $\delta = 2.77$ (s, 3H, CH_3), 2.86 (t, $J = 6.9$ Hz, 2H, CH_2-CH_2), 2.99 (t, $J = 6.6$ Hz, 2H, CH_2-CH_2), 4.19 (s, 2H, CH_2CN), 7.26 – 7.96 (m, 4H, arom. H). – ^{13}C NMR ($CDCl_3$): $\delta = 16.70$, 18.85 (benzindazole C-4, C-5), 23.50 (CH_3), 28.95 (CH_2CN), 115.54 (C≡N), 123.64, 127.37, 128.75, 129.78 (arom. CH), 121.78, 127.74, 128.94, 137.93 (arom. quaternary C), 172.03 (CO). – MS: m/z (%) = 251 (66)[M^+], 209 (100), 208 (12), 182 (22), 181 (33). $C_{15}H_{13}N_3O$ (251.27): calcd. C 71.70, H 5.21, N 16.72; found C 71.74, H 5.25, N 16.77.

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