Functionally substituted arylhydrazones as building blocks in heterocyclic synthesis: routes to pyridazines and pyridazinoquinazolines

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Abstract
The arylhydrazones 2a-c were prepared via coupling acetoacetic acid with aromatic diazonium salts. These arylhydrazones condensed with ethyl cyanoacetate and malononitrile to yield the acyclic product 4 which cyclised only after long reflux into the pyridazines 5 or 6,11-dihydropyridazino[1,6-a]quinazoline-4-carbonitrile 6 depending on the nature of substituent on the aryl moiety. Compound 2b and 2c reacted with α,β-unsaturated nitriles 7 to yield the pyridazinoquinazoline 13 and 16 respectively.

Keywords: Azaenamines, pyridazines, pyridazinoquinazolines

Introduction
The chemistry and pharmacology of pyridazines has recently received considerable interest. This can be readily realized from vast number of papers and patents dealing with synthesis 1-5, chemistry 6-8, and biological activities of pyridazine derivatives 9,10. In the last few years we have been involved in a programme aimed at developing efficient syntheses of pyridazines and fused pyridazines 11-14 utilizing functionally substituted arylhydrazones precursors. In conjunction of this work we report here routes to pyridazinones, and pyridazinoquinazolines utilizing the readily obtainable 2a-c as starting materials.

Results and Discussion
Coupling acetoacetic acid with the diazonium salts 1a-c has afforded the corresponding pyruvaldehyde arylhydrazones 2a-c in 74-90.8 % yields. Although it seemed logical to assign to syn structure 3 for these compounds based on observed low field NH signal that is attributable to
deshielding by hydrogen bonding, X-ray crystal structure of 2a (figure 1) indicated that it exists in the antiform 2a. The low field hydrazone NH at δ 12 ppm is not thus due to deshielding by hydrogen bonding as has been claimed earlier but most likely resulted from delocalization of nitrogen lone pair (C.f. Scheme 1 structure 2a(II)). Although, possible hydrogen bonding of hydrazone NH with DMSO cannot be overlooked.

Scheme 1

Figure 1. X-ray structure of compound 2a
Table 1. Selected bond lengths and bond angles for compound 2a

<table>
<thead>
<tr>
<th>Bond</th>
<th>Bond length</th>
<th>Bond</th>
<th>Bond angle</th>
</tr>
</thead>
<tbody>
<tr>
<td>N1-N2</td>
<td>1.335</td>
<td>N2-N1-C8</td>
<td>117.8</td>
</tr>
<tr>
<td>N1-C8</td>
<td>1.285</td>
<td>N1-N2-C5</td>
<td>121.6</td>
</tr>
<tr>
<td>N2-C5</td>
<td>1.395</td>
<td>N2-C5-C4</td>
<td>122.4</td>
</tr>
<tr>
<td>C8-C9</td>
<td>1.450</td>
<td>O3-C9-C8</td>
<td>118.9</td>
</tr>
</tbody>
</table>

Compound 2b condensed with ethyl cyanoacetate 3a to yield the acyclic condensation product 4b which cyclised into pyridazine 5b only on long reflux in acetic acid. This is in contrast to the behavior of 2a, where the acyclic intermediate 4a could never be isolated, on reacting it with 3a [15]. In contrast to the behavior of 2a,b, compound 2c condenses with ethyl cyanoacetate to yield acyclic product 4c, which failed to cyclise into pyridazine 5c under a variety of conditions. The difference in behavior between 2a,b and 2c toward ethyl cyanacetate is believed to result from interaction with the ester function and hydrazone nitrogen which is involved in hydrogen bonding with ester function. $^1$H NMR indicates that 4b,c exist as a mixture of cis and trans forms I and II. Thus two overlapping triplets for CH$_3$ ester and two overlapping quartets for CH$_2$ were observed. Aromatic protons revealed expected pattern. Azomethine CH appeared as two signals and it is difficult to assign which CH for which isomer as complex factors are involved in this situation. Compound 2c also condensed with malononitrile 3b to yield the acyclic product 4d which then cyclises into pyridazinoquinazoline derivative 6 via intermediacy of 5d.

Scheme 2
Compounds 5a,b react readily with α-substituted cinnamionitriles 7a-c to yield acyclic intermediate 8 that readily cyclized into phthalazine derivatives 9a-c via hydrogen cyanide elimination. These same products were obtained from reaction of compounds 4b-d with α-substituted cinnamionitriles. It is believed that compounds 4 are initially cyclised into pyridazines 5 under reaction conditions which then reacts with α-cinnamionitriles to give the targeted molecule. (C.f. scheme 3)

\[
\begin{align*}
\text{4 or 5} & \quad \text{Ar} = \text{C}_6\text{H}_5; \quad R = \text{CN} \\
7a & \quad \text{Ar} = \text{C}_6\text{H}_5; \quad R = \text{CN} \\
b & \quad \text{Ar} = \text{C}_6\text{H}_5\text{Cl}(p); \quad R = \text{CN} \\
c & \quad \text{Ar} = \text{C}_6\text{H}_5; \quad R = \text{COOEt} \\
d & \quad \text{Ar} = \text{C}_6\text{H}_5; \quad R = \text{COPh} \\
\end{align*}
\]

\[
\begin{align*}
9a & \quad X = \text{H} ; \quad \text{Ar} = \text{C}_6\text{H}_5; \quad R = \text{CN}; \quad Z = \text{O} \\
b & \quad X = \text{H} ; \quad \text{Ar} = \text{C}_6\text{H}_5; \quad R = \text{COOEt}; \quad Z = \text{O} \\
c & \quad X = \text{CN}; \quad \text{Ar} = \text{C}_6\text{H}_5\text{Cl}(p); \quad R = \text{CN}; \quad Z = \text{O} \\
d & \quad X = \text{COOMe}; \quad \text{Ar} = \text{C}_6\text{H}_5\text{Cl}(p); \quad R = \text{CN}; \quad Z = \text{O} \\
e & \quad X = \text{COOMe}; \quad \text{Ar} = \text{C}_6\text{H}_5; \quad R = \text{COOEt}; \quad Z = \text{O} \\
f & \quad X = \text{COOMe}; \quad \text{Ar} = \text{C}_6\text{H}_5\text{Cl}(p); \quad R = \text{CN}; \quad Z = \text{NH} \\
\end{align*}
\]

\[
\begin{align*}
\text{Scheme 3} \\
\text{It has recently been shown that aldehydehydrazone CH is electron rich and reacts with electrophiles}^{16-18}. \text{Although it was proposed that presence of electron donating substituents at hydrazone nitrogen is necessary to maintain reactivity, we could show very recently that aryl hydrazones are also sufficiently reactive toward electrophiles under relatively mild conditions}^{18}. \text{The reactivity of 2a toward α,β-unsaturated nitriles has recently been utilized by us to construct a new synthetic approach for 1,4-dihydro-6-aminopyridazines}^{13}. \text{In the present work we would like to show that even 2b,c with electron attracting substituents on aryl moiety are also reactive toward electrophiles. Thus reacting 2b with p-chlorobenzylidenemalononitrile 7b, ethyl benzylidenecyanoacetat 7c, and 2-benzoyl-3-phenylacrylonitrile 7d has resulted in formation of 1:1 adduct that can in theory be assigned structures 10-13. Structure 13a was readily established based on }^{13}\text{C NMR that revealed presence of methyl signal at }\delta 25.21\text{ppm and only one cyano carbon at }\delta 112.08\text{ ppm. The structures of 13b,c were elucidated based on IR and NMR where IR spectra revealed the absence of CN signals We believe that initially 11 is formed and cyclized into 12 which then cyclized into 13. (C.f. Scheme 4).}
\end{align*}
\]
Scheme 4

In contrast to this 2c reacted with 7b to yield a product 14 that could not be identified. On the other hand, the reaction of 2c with 7c results in the formation of product of cyclization with methanol elimination to give compound 16. The structure of 16 was elucidated based on IR which indicated the absence of CN band, $^1$H NMR which indicated the absence of OCH$_3$ signal, and $^{13}$C NMR spectra which indicated the absence of any CN and OCH$_3$ bands and signals. (C.f. scheme 5).

Scheme 5
Conclusions

We could show that Pyruvaldehyde-1-arylhydrazones 2a-c are valuable precursors to polyfunctionally substituted pyridazines, and pyridazinoquinazoline, moreover we could clearly show that hydrazone CH in 2 is activated toward electrophiles and thus can undergo Michael addition to α-substituted cinnamonicnitriles under mild conditions.

Experimental Section

General Procedures. All melting points were determined on a Stuart melting point apparatus and are uncorrected. The $^1$H and $^{13}$C NMR spectra (300 MHz) were recorded on Varian Gemini NMR spectrometer. Chemical shifts (δ) are given from TMS (0 ppm) as internal standard for $^1$H-NMR and $^{13}$C-NMR. Mass spectra were measured on a Shimadzu GMMS -QP-1000 EX mass spectrometer at 70 eV. The elemental analyses were performed at the micro analytical center, Cairo University. The IR spectra were recorded in KBr using a FTIR unit Bruker-vector 22 spectrophotometer. The crystal structure was determined by the X-ray unit at the National Research Center, Dokki, Cairo.

Crystallographic analysis for compound 2a. The crystals were mounted on a glass fiber. All measurements were performed on an ENRAF NONIUNS FR 590. The data were collected at temperature 20 ± 1 °C using the ω scanning technique to a maximum of 20 of 27.12°. The temperature was solved by direct method using SIR 92 and full-matrix least squares. Nonhydrogen atoms were refined anisotropically. Hydrogen atoms were located geometrically and were refined isotropically.

Crystal data. C$_9$H$_{10}$N$_2$O, M = 162.19, monoclinic, a = 5.4337 (2), b = 10.1221 (5), c = 16.1178 (10) Å, α = γ = 90.00°, β = 10.18 (10°) *10$^{10}$ space group: P2$_1$/c. Z =4, D$_x$ = 1.236 Mg m$^{-3}$, reflection 871 measured, θ$_{max}$ = 25.03°, oR factor = 0.108

General procedures for preparation of arylhydrazonopropan-2-one (2) ref. 19 A mixture of KOH (3.5 g) in 100 ml of water, and 6.5 ml of ethyl acetoacetate was allowed to stir at room temperature for 24 hours. This solution is then cooled at 0 °C temperature and then acidified with 4.5 ml of Conc..HCl in 15 ml of ice water. The resulting solution is the treated with aryldiazonium chloride (prepared from the corresponding aromatic amine (0.05 mol) and the appropriate quantities of both HCl and sodium nitrite). The mixture is made basic by addition of 8.0 g of sodium acetate. The solid product, so formed was collected by filtration.

(Phenyl-hydrazono)-propan-2-one (2a). ref. 19 Yield 1.2 g (74 %) as a solid, which was recrystallized from toluene to give yellow crystals (m.p 148-150) °C [lit. m.p. = 148 °C]; Anal. Calcd. for C$_9$H$_{10}$N$_2$O (162.19): C, 66.65; H, 6.21; N, 17.27. Found: C, 66.43; H, 6.05; N, 17.15. IR (KBr, cm$^{-1}$): 3249.6 (NH), 1649.58 (CO); $^1$H NMR (300 MHz, DMSO-d$_6$): δ, ppm: 2.32 (s, 3H, CH$_3$), 6.93 (s, 1H, vinyl-H), 6.95-7.339 (m, 5H, Ph-H), 11.33 (s, 1H, NH); MS (EI): m/z (%) = 162 (M$^+$).
2-\([N''-(2-Oxo-propylidene)-hydrazino]-benzonitrile\) (2b). Yield 1.4 g (74.8%) as a solid, which was recrystallized from ethanol as white solid (m.p: 122-124 °C). *Anal.* Calcd. for C\(_{10}\)H\(_9\)N\(_3\)O (187.20): C, 64.16; H, 4.97; N, 22.45. Found: C, 64.45; H, 4.92; N, 22.67. IR (KBr, cm\(^{-1}\)): 3256.8 (NH), 2222 (CN), 1675 (CO). \(^1\)H MNR (300 MHz, DMSO-d\(_6\)): \(\delta\), ppm 2.36 (s, 3H, CH\(_3\)), 7.05-7.11 (m, 1H, Ar-H5), 7.37 (d, 1H, Ar-H6), 7.47 (s, 1H, vinyl-H), 7.59 (m, 1H, Ar-H4), 7.68 (d, 1H, Ar-H3), 11.51 (s, 1H, NH); MS (EI): m/z (%) = 187 (M\(^+\)).

2-\([N''-(2-Oxo-propylidene)-hydrazino]-benzoic acid methyl ester\) (2c). Yield 2 g (90.8%) as a solid which was recrystallized from ethanol as white solid (m.p: 99-101 °C). *Anal.* Calcd. for C\(_{11}\)H\(_{12}\)N\(_2\)O\(_3\) (220.23): C, 59.99; H, 5.49; N, 12.72. Found: C, 60.20; H, 5.67; N, 12.59. IR (KBr, cm\(^{-1}\)): 3248.3 (NH), 1677.7, 1593 (CO). \(^1\)H MNR (300 MHz, DMSO-d\(_6\)): \(\delta\), ppm 2.35 (s, 3H, CH\(_3\)), 3.87 (s, 3H, OCH\(_3\)), 7.00-7.06 (m, 1H, Ar-H5), 7.6 (s, 1H, vinyl-H), 7.60-7.63 (m, 1H, Ar-H4), 7.89 (d, 1H, Ar-H6) 11.37 (s, 1H, NH). MS (EI): m/z (%) = 220 (M\(^+\)).

**General method for preparation of 4b and 4c.** A mixture of 2b or 2c (0.01 mol), ethyl cyanoacetate (0.01 mol), and ammonium acetate (2g) in acetic acid (20 ml) was heated at 200 °C for 5 min, then left to cool and poured onto water. The solid product obtained was crystallized from ethanol.

2-Cyano-4-\([2-cyano-phenyl]-hydrazono\)-3-methyl-but-2-enolic acid ethyl ester (4b). Yield 2.5 g (88.65%) (m.p: 128-130 °C). *Anal.* Calcd. for C\(_{15}\)H\(_{14}\)N\(_4\)O\(_2\) (282.30): C, 63.82; H, 5.00; N, 19.85. Found: C, 63.72; H, 4.83; N, 19.62. IR (KBr, cm\(^{-1}\)): 3245.2 (NH), 2228.5 (CN), 1722.5 (CO) \(^1\)H MNR (300 MHz, DMSO-d\(_6\)): \(\delta\), ppm 1.28 (2 t, 3H, CH\(_3\), \(J = 7.2\) Hz), 2.57 (s, 3H, CH\(_3\)), 4.27 (2 q, 2H, CH\(_2\), \(J = 7.2\) Hz), 7.08-7.71 (m, 4H, Ar-H), 8.44 (s, 0.48 H, vinyl-H), 9.11 (s, 0.52 H, vinyl-H), 11.99 (s, 1H, NH). MS (EI): m/z (%) = 282 (M\(^+\)).

2-\([N''-(3-cyano-3-ethoxycarbonyl-2-methyl-allylidene)-hydrazino]-benzoic acid methyl ester\) (4c). Yield 2.72 g (86.26%) (m.p: 142-144 °C). *Anal.* Calcd. for C\(_{16}\)H\(_{17}\)N\(_3\)O\(_4\) (315.33): C, 60.94; H, 5.43; N, 13.33. Found: C, 60.82; H, 5.62; N, 13.61. IR (KBr, cm\(^{-1}\)): 3446.8 (NH), 2211.1 (CN), 1718 , 1681 (CO). \(^1\)H MNR (300 MHz, DMSO-d\(_6\)): \(\delta\), ppm 2.48 (s, 3H, CH\(_3\)), 3.89 (s, 3H, OCH\(_3\)), 7.10-7.90 (m, 4H, Ar-H), 8.40 (s, 1H, vinyl-H), 11.85 (s, 1H, NH). MS (EI): m/z (%) = 315 (M\(^+\)).

**Preparation of 2-\([N''-(3,3-dicyano-2-methyl-allylidene)-hydrazino]-benzoic acid methyl ester\) (4d).** A mixture of 2c (10 mmol), and malononitrile was refluxed in ethanol (20 ml) in presence of piperidine for 5 min. The solvent was evaporated under vacuum and the crude product was collected and crystallized from ethanol / Dioxan.

Yield 2.32 g (86.48%); m.p: 212-214 °C. *Anal.* Calcd. for C\(_{14}\)H\(_{12}\)N\(_4\)O\(_2\) (268.28): C, 62.68; H, 4.51; N, 20.88. Found: C, 62.42; H, 4.72; N, 20.61. IR (KBr, cm\(^{-1}\)): 3231.4 (NH), 2218.9 (CN), 1691.9 (CO). \(^1\)H MNR (300 MHz, DMSO-d\(_6\)): \(\delta\), ppm 2.48 (s, 3H, CH\(_3\)), 3.89 (s, 3H, OCH\(_3\)), 7.10-7.90 (m, 4H, Ar-H), 8.40 (s, 1H, vinyl-H), 11.85 (s, 1H, NH) \(^{13}\)C MNR (300 MHz, DMSO-d\(_6\)): \(\delta\), ppm 16.88 (CH\(_3\)), 52.34 (OCH\(_3\)), 79.87 (C-CN), 112.67, 113.76 (CN), 113.96, 115.49,
122.05, 130.84, 134.54, 135.44 (CH-Ar), 143.66 (CH-vinyl), 166.79 (C-CH₃), 168.07 (COOCH₃). MS (EI): m/z (%) = 268 (M⁺).

**General method for preparation of 5a,b.** A mixture of each of 2a or 2b (0.01 mol), ethyl cyanoacetate (0.01 mol), and ammonium acetate (2g) in acetic acid (20 ml) was heated under reflux for 3 hours, then left to cool and poured onto water. The solid product obtained was crystallized from ethanol.

**4-Methyl-6-oxo-1-phenyl-1,6-dihydropyridazine-5-carbonitrile (5a).** Yield 1.82 g (86.16%) (m.p: 158-160 °C). *Anal. Calcd. for C₁₂H₉N₃O (211.23): C, 68.24; H, 4.29; N, 19.89. Found: C, 68.16; H, 4.14; N, 19.89.* IR (KBr, cm⁻¹): 2233 (CN), 1659.4 (CO). ¹H MNR (300 MHz, DMSO-d₆): δ, ppm 2.47 (s, 3H, CH₃), 7.54 - 7.55 (m, 5H, Ar-H), 8.25 (s, 1H, pyridazine-H). ¹³C MNR (300 MHz, DMSO-d₆): δ, ppm 19.12 (CH₃), 114.06 (C-CN), 114.48 (CN), 126.59, 126.83, 129.77, 129.88 (CH-Ar), 139.91 (CH-pyridazine), 141.60 (C-CH₃), 157.08 (CO). MS (EI): m/z (%) = 211 (M⁺).

**1-(2-Cyano-phenyl)-4-methyl-6-oxo-1,6-dihydropyridazine-5-carbonitrile (5b).** Yield 2.0 g (84.47%) (m.p: 170-172 °C). *Anal. Calcd. for C₁₃H₈N₄O (236.23): C, 66.10; H, 3.41; N, 23.72. Found: C, 66.26; H, 3.54; N, 23.85.* IR (KBr, cm⁻¹): 2232.8 (CN), 1665.8 (CO). ¹H MNR (300 MHz, DMSO-d₆): δ, ppm 2.52 (s, 3H, CH₃), 7.71-7.76 (m, 2H, Ar-H₃,4), 7.93 (m, 1H, Ar-H₅), 8.09 (d, 1H, Ar-H₆), 8.34 (s, 1H, pyrimidine-H). MS (EI): m/z (%) = 236 (M⁺).

**Preparation of 3-methyl-6-oxo-6,11-dihydropyridazino[1,6-a]quinazoline-4-carbonitrile (6).** A mixture of 2c (10 mmol), and malononitrile was refluxed in ethanol (20 ml) in presence of piperidine for 30 min. The solvent was evaporated under vacuum and the crude product was collected and crystallized from Dioxan.

Yield 2.1 g (88.9%) (m.p: 280-282 °C). *Anal. Calcd. for C₁₃H₈N₄O (236.23): C, 66.10; H, 3.41; N, 23.72. Found: C, 66.23; H, 3.52; N, 23.61.* IR (KBr, cm⁻¹): 2232.9 (CN), 1655 (CO). ¹H MNR (300 MHz, DMSO-d₆): δ, ppm 2.61 (s, 3H, CH₃), 7.72-8.39 (m, 4H, Ar-H), 8.78 (s, 1H, pyridazine-H). MS (EI): m/z (%) = 236 (M⁺).

**General procedure for preparation of phthalazines 9a-f.** *Methode A.* A mixture of 4 (or 5) (10 mmol), and benzylidene derivatives 7 was refluxed in ethanol (20 ml) in presence of piperidine for 2 h. The solvent was evaporated under vacuum and the crude product was collected and crystallized from ethanol.

**5-amino-4-oxo-3,4-dihydro-phthalazine-6-carbonitrile (9a).** Yield 3.20 g (80.40%); m.p: 288-290 °C. *Anal. Calcd. for C₂₁H₁₄N₄O (338.37): C, 74.54; H, 4.17; N, 16.56. Found: C, 74.62; H, 4.24; N, 16.71.* IR (KBr, cm⁻¹): 3453.4, 3300.4 (NH₂), 2207.1 (CN), 1657.2 (CO). ¹H MNR (300 MHz, CDCl₃): δ, ppm 6.92 (s, 1H, Ar-H), 7.28 (br s, 2H, NH₂), 7.43-7.64 (m, 10H, Ar-H) 8.17 (s, 1H, pyridazine-H). ¹³C MNR (300 MHz, CDCl₃): δ, ppm 96.48 (C-CN), 110.48 (CN), 113.85, 117, 126.4, 128.91, 129.06, 129.36, 129.05, 129.56, 130.23, 134.25, 138.17, 139.25, 141.69 (CH-Ar), 151.51(C-NH₂), 154.21(CH-pyridazine), 161.02 (CO). MS (EI): m/z (%) = 338 (M⁺).
5-Amino-4-oxo-3,7-diphenyl-3,4-dihydro-phthalazine-6-carboxylic acid ethyl ester (9b). Yield 33.2 g (86.1%) (m.p: 112-114 °C). Anal. Calcd. for C_{23}H_{19}N_{3}O_{3} (385.43): C, 71.68; H, 4.97; N, 10.81. IR (KBr, cm\(^{-1}\)): 3432.3, 3293.6 (NH\(_2\)), 1688.1, 1640.6 (CO). \(^1\)H MNR (300 MHz, DMSO-d\(_6\)): \(\delta\), ppm 0.77 (t, 3H, CH\(_3\), \(J = 7.2\) Hz), 3.96 (q, 2H, CH\(_2\), \(J = 7.2\) Hz), 6.97 (s, 1H, Ar-H), 7.32-7.62 (m, 10H, Ar-H), 7.84 (br s, 2H, pyridazine-H). \(^13\)C MNR (300 MHz, DMSO-d\(_6\)): \(\delta\), ppm 13.11 (CH\(_3\)), 60.69 (CH\(_2\)), 113.7 (C-COOEt), 114.0, 125.73, 126.19, 127.64, 127.88, 128.33, 128.55, 128.64, 132.17, 139.19, 140.95, 141.66 (CH-Ar), 148.12 (C-Ph), 149.75 (C-NH\(_2\)), 160.63 (CH-pyridazine), 167.42 (CO). MS (EI): m/z (%) = 385 (M\(^+\)).

5-amino-7-(4-chloro-phenyl)-3-(2-cyano-phenyl)-4-oxo-3,4-dihydro-phthalazine-6-carbonitrile (9c). Yield 3.20 g (80.4%); m.p: 288-290 °C. Anal. Calcd. for C\(_{22}\)H\(_{12}\)ClN\(_5\)O (397.83): C, 66.42; H, 3.04; N, 17.60. IR (KBr, cm\(^{-1}\)): 3471.9, 3332.1 (NH\(_2\)), 2208.8 (CN), 1656.1 (CO). \(^1\)H MNR (300 MHz, DMSO-d\(_6\)): \(\delta\), ppm 7.18 (s, 1H, Ar-H), 7.63-7.95 (m, 8H, Ar-H), 8.07 (s, 2H, NH\(_2\)), 8.52 (s, 1H, pyridazine-H). MS (EI): m/z (%) = 397 (M\(^+\)).

2-[8-Amino-6-(4-chloro-phenyl)-7-cyano-1-oxo-1H-phthalazin-2-yl]-benzoic acid methyl ester (9d). Yield 3.52 g (81.7%) (m.p: 295-297 °C). Anal. Calcd. for C\(_{23}\)H\(_{15}\)ClN\(_4\)O\(_3\) (430.85): C, 64.12; H, 3.51; N, 13. Found: C, 64.25; H, 3.42; N, 12.92. IR (KBr, cm\(^{-1}\)): 3437.7, 3356.2 (NH\(_2\)), 2213.9 (CN), 1686.8, 1651.3 (CO). \(^1\)H MNR (300 MHz, DMSO-d\(_6\)): \(\delta\), ppm 3.87 (s, 3H, CH\(_3\)), 6.73 (br s, 2H, NH\(_2\)), 6.90-7.87 (m, 9H, Ar-H), 8.31 (s, 1H, pyridazine-H). MS (EI): m/z (%) = 430 (M\(^+\)).

5-Amino-3-(2-methoxycarbonyl-phenyl) -4-oxo-7-phenyl-3,4-dihydro-phthalazin-6-carboxylic acid ethyl ester (9e). Yield 3.51 g (79.15%) (m.p: 158-160 °C). Anal. Calcd. for C\(_{25}\)H\(_{21}\)N\(_3\)O\(_5\) (443.46): C, 67.71; H, 4.77; N, 9.48. IR (KBr, cm\(^{-1}\)): 3459.8, 3310.1 (NH\(_2\)), 1728, 1691.5, 1641.5 (CO). \(^1\)H MNR (300 MHz, DMSO-d\(_6\)): \(\delta\), ppm 0.75 (t, 3H, CH\(_3\), \(J = 7.2\) Hz), 3.66 (s, 3H, CH\(_3\)), 3.95 (q, 2H, CH\(_2\), \(J = 7.2\) Hz), 7.01 (s, 1H, Ar-H), 7.34 (br s, 2H, NH\(_2\)), 7.43-7.97 (m, 9H, Ar-H), 8.36 (s, 1H, pyridazine-H). MS (EI): m/z (%) = 443 (M\(^+\)).

2-[8-Amino-6-(4-chloro-phenyl)-7-cyano-1-imino-1H-phthalazin-2-yl]-benzoic acid methyl ester (9f). Yield 3.31 g (77%) (m.p: 320 °C). Anal. Calcd. for C\(_{23}\)H\(_{16}\)ClN\(_5\)O\(_2\) (429.87): C, 64.27; H, 3.75; N, 16.29. IR (KBr, cm\(^{-1}\)): 3432.3, 3353, 3246.3 (NH\(_2\)), 2212.9 (CN), 1685.5 (CO). \(^1\)H MNR (300 MHz, DMSO-d\(_6\)): \(\delta\), ppm 3.88 (s, 3H, CH\(_3\)), 6.74 (m, 11H, Ar-H and NH\(_2\)), 8.32 (s, 1H, pyridazine-H), 11.41 (s, 1H, NH). MS (EI): m/z (%) = 429 (M\(^+\)).

General procedures for preparation of triaza-phenanthrenes 13a-c and 16. Methode A. A mixture of azaenamine 2b or 2c (10 mmol), and benzylidene derivatives 6a-c was refluxed in pyridine (20 ml) for 2 h. , then poured onto water and acidified with dilute hydrochloric acid. The solid product obtained was crystallized from ethanol.

Methode B. A solution of each of 2b or 2c (10 mmol) was treated with the benzylidene 7a-c (10
mmol) in pyridine (2 ml) was irradiated in microwave oven for two minutes, then poured onto water and acidified with dilute hydrochloric acid. The solid product obtained was crystallized from ethanol.

2-Acety;-6-amino-3-(4-chlorophenyl)-3,11-dihydro-pyridazino[1,6-a]quinazoline-4-carbonitrile (13a). Yield 3.15 g (83.82%); m.p: 230-232 °C. Anal. Calcd. for C_{20}H_{14}ClN_{5}O (375.82): C, 63.92; H, 3.75; N, 18.63. Found: C, 63.63; H, 3.69; N, 3.84. IR (KBr, cm\(^{-1}\)): 3435.8, 3425.1 (NH\(_2\)), 2223 (CN), 1687 (CO). \(^1\)H MNR (300 MHz, DMSO-d\(_6\)): \(\delta\), ppm 2.47 (s, 3H, CH\(_3\)), 4.9 (s, 1H, pyridazine-H), 7.18(s, 2H, NH\(_2\)), 7.29-8.15 (m, 8H, Ar-H). \(^1\)C MNR (300 MHz, DMSO-d\(_6\)): \(\delta\), ppm 25.21 (CH\(_3\)), 37.28(CH pyridazine), 67.65(C-CN), 112.08(CN), 114.44, 120.48, 124.15, 124.72, 128.89, 129.25, 132.12, 134.43, 139.94, 141.37 (CH-Ar), 144.68(C-COCH\(_3\)), 147.30 (C6-pyridazine), 156.39(C- NH\(_2\)), 195.72 (CO). MS (EI): m/z (%) = 375 (M\(^+\)).

Ethyl-2-Acety-6-amino-3-phenyl-3,11-dihydro-pyridazino[1,6-a]quinazoline-4-carboxylate (13b). Yield 3.15 g (83.82%) (m.p: 194-196 °C). Anal. Calcd. for C\(_{22}\)H\(_{20}\)N\(_4\)O\(_3\) (388.43): C,68.03; H, 5.19; N, 14.42. Found: C, 68.22; H, 5.23; N,14.36. IR (KBr, cm-1): 3490.9, 3375.2 (NH\(_2\)), 1681.8 (CO). \(^1\)H MNR (300 MHz, DMSO-d\(_6\)): \(\delta\), ppm 1.19 (t, 3H, CH\(_3\), \(J\) = 6.9 Hz), 2.53 (s, 3H, CH\(_3\)), 4.06(q, 2H, CH\(_2\), \(J\) = 6.9 Hz), 5.34 (s, 1H, pyridazine-H), 7.06 (s, 2H, NH\(_2\)), 7.20-8.06 (m, 9H, Ar-H). MS (EI): m/z (%) = 388 (M\(^+\)).

2-Acety;-6-oxo-3-phenyl-3,5,6,11-tetrahydro-pyridazino[1,6-a]quinazoline-4-carboxylate (16). Yield 3.12 g (80.12%) (m.p: 206-208 °C). Anal. Calcd. for C\(_{22}\)H\(_{19}\)N\(_3\)O\(_4\) (389.41): C,67.86; H, 4.92; N, 10.79. Found: C, 67.78; H, 4.83; N,10.67. IR (KBr, cm\(^{-1}\)): 3432 (NH), 1718, 1695.5, 1639 (CO). \(^1\)H MNR (300 MHz, DMSO-d\(_6\)): \(\delta\), ppm 2.48 (s, 3H, CH\(_3\)), 4.09 (q, 2H, CH\(_2\), \(J\) = 7.2 Hz), 7.18 (s, 2H, NH\(_2\)), 7.24-8.01 (m, 9H, Ar-H). MS (EI): m/z (%) = 389 (M\(^+\)).

References


5. MERCK & CO INC (US); LEBSACK ALECD (US); MUNOZ BENITO (US); PRACITTO RICHARD (US); VENKATRAMAN SHANKAR (US); WANG BOWEI (US); GUNZNER JANET (US), European, **2005**, patent number (WO2005041971), priority number (US20030513046p 20031021.


