1H-Benzo[de]cinnolines: an interesting class of heterocycles

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Dedicated to our friend Joan Bosch, Professor of the University of Barcelona, on his 75th birthday

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Abstract

1H-Benzo[de]cinnolines, 6H-dibenzo[de,g]cinnolines and 1H-indeno[6,7,1-def]cinnolines are an interesting class of heterocyclic compounds related both to perimidines and to indazoles. This review covers the bibliography from their discovery in 1971 to the present days. Synthesis, reactivity and physico-chemical properties are reported in their integrity as well as theoretical calculations. Up to now, there are almost no biological studies.

Keywords: 1H-Benzo[de]cinnolines, 1H-indeno[6,7,1-def]cinnolines, perimidines, protonation, tautomerism
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1. Introduction

Compared to perimidines 2,1-3 1H-benz[de]cinnolines 1 have been much less studied; they have a similar relationship than that between benzimidazoles 4 and indazoles 3 (Figure 1).

![Figure 1](image-url)

**Figure 1.** Relationship between benzazoles and naphthoazines.

In the Web of Science (WoS)4 and ScienceDirect databases, the number of entries on perimidines (2 and derivatives) and benzo[de]cinnolines (1 and derivatives) is very different (Table 1); the same happens for benzimidazoles (4) and indazoles (3). This is partly due to the fact that o-phenylenediamine and 1,8-diaminonaphthalene are cheap and convenient starting materials; note however that the difference is much larger in the 2/1 pair than in the 4/3 pair, as a consequence that benzo[de]cinnolines have been reported with different names, such as diazaphenalenones, peridazines, etc. The main contribution to both benzo[de]cinnolines and perimidines came from two groups of the Southern Federal University (Rostov-on-
Don, Russia); Pozharskii’s group in the field of perimidines 2, 105 references out of 387 are from his group in our 2020 review; analogously, Mezheritskii group in the field of benzo[de]cinnolines 1, 15 references out of 51 are from his group in the present review.

**Table 1. Number of references cited in the literature**

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<thead>
<tr>
<th></th>
<th>Web of Science</th>
<th>ScienceDirect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benzimidazoles 4</td>
<td>38,906</td>
<td>31,841</td>
</tr>
<tr>
<td>Indazoles 3</td>
<td>5,530</td>
<td>5,223</td>
</tr>
<tr>
<td>Ratio 4/3</td>
<td>7.0</td>
<td>6.1</td>
</tr>
<tr>
<td>Perimidines 2</td>
<td>211</td>
<td>287</td>
</tr>
<tr>
<td>Benzo[de]cinnolines 1</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Ratio 2/1</td>
<td>70.3</td>
<td>71.8</td>
</tr>
</tbody>
</table>

2. **Synthetic Methodologies**

Simple 1H-benzo[de]cinnolines have been prepared by Lacy and Smith, Scheme 1(a)\(^5\) and 1(b),\(^6\) and by Aksenov, Aksenova \textit{et al.},\(^7\) Scheme 1(c).

**Scheme 1. Synthesis of simple 1H-benzo[de]cinnolines.**

Using the methods represented in Scheme 1(a), a series of 1H-benzo[de]cinnolines have been prepared (Figure 2) by Mezheritskii \textit{et al.},\(^8-13\) who isolated the intermediate hydrazones linking 5 to 6.
Figure 2. 1H-benzo[de]cinnolines prepared according to the method described in 1(a).

A totally different method has been reported by Chenoweth et al.,8 (cited in 9). A very complex and beautiful reaction, starting from 3,6-dimethyl-1,2,4,5-tetrazine and o-benzyne, allows to prepare compound 20, 4-methyl-6-phenyl-6H-dibenzo[de,g]cinnolin10. They have prepared a large set of compounds, 20-32, and some dimethyl derivatives starting from 4,5-dimethyl-o-benzyne (Scheme 2).

Scheme 2. Synthesis of 6H-dibenzo[de,g]cinnolines; for compound 20, the benzo[de]cinnoline skeleton is shown in red.
3. Reactivity of 1H-Benz[de]cinnolines

3.1. Tautomerism

3.1.1. Annular tautomerism. Here appears a first important difference between the two series of benzazoles and naphthoazines (Figure 3). In the case of the benzimidazole 4/perimidine 2 pair there is a perfect similitude, both presenting annular tautomerism of the class called degenerate or autotrope, indicating that both tautomers are identical.11 In the case of indazole 3, annular tautomers, 1H and 2H, are of different energy.12,13

![Figure 3](image)

**Figure 3.** The prototropic relationships in compounds 1 to 4.

In N-unsubstituted benz[de]cinnolines 1, the transfer of the proton from N1 to N2 led to a zwitterionic compound (in blue in Figure 3). Analogously of all other compounds of Figure 3, the 1H-benz[de]cinnoline have also CH tautomers that are much less stable because the aromaticity is totally or partially lost. A recent work14 where theoretical B3LYP/6-311++G(d,p) calculations15,16 were carried out using the Gaussian 16 set of programs17 including general solvent effects (PCM method)18 resulted in the data depicted in Figure 4.

![Figure 4](image)

**Figure 4.** Relative energies (E<sub>rel</sub> in kJ·mol<sup>-1</sup>) of the eight tautomers of benz[de]cinnoline 6c (1) in the gas-phase//in water.
1. Water vs. gas: $E_{\text{rel water}} = -(6.7 \pm 2.7) + (0.96 \pm 0.02) E_{\text{rel gas}}, n = 8, R^2 = 0.996$

The fact that the solvation by water leads to values roughly proportional to the gas values allow to discuss only the $E_{\text{rel gas}}$ values.

2. The zwitterion $2\text{H}$ although highly unstable compared with the $1\text{H}$ tautomer is still more stable than any CH tautomer.

3. The two most stable CH tautomers are $7\text{H}$ and $9\text{H}$. The $9\text{aaH}$-tautomer is very unstable due to the destruction of the aromaticity of two benzene rings.

3.1.2. Functional tautomerism. Similarly to indazolinones\textsuperscript{19-21} 3-hydroxy-$1\text{H}$-benzo[de]cinnolines can present functional tautomerism between an oxo-tautomer $33$ (1-methyl-1,2-dihydro-$3\text{H}$-benzo[de]cinnolin-3-one) and the corresponding hydroxy-tautomer $34$ (1-methyl-$1\text{H}$-benzo[de]cinnolin-3-ol); however, the only reported compounds are analogs of 1,2-dimethyl-1,2-dihydro-$3\text{H}$-benzo[de]cinnolin-3-one ($35$) which has a fixed oxo-structure; so far, compounds $33$-$35$ have not been reported in the literature. The only reported compounds $36$ and $37$ are analogs of $35$; the X-ray structures of $36$, HIPIT, and $37$, HIPPOL, have been determined\textsuperscript{19,20} (Figure 5).

![Figure 5. The tautomerism of $1\text{H}$-benzo[de]cinnolones.](image)

3.2. Acidity and basicity

Figure 6 compares indazoles and benzo[de]cinnolines in what acidity and basicity are concerned. The anions are similar but the cations are different, the most stable protonated form of $6\text{c}$ is the C-protonated $8\text{cH}^+$ (in red) and not the N2-protonated $6\text{cH}^+$ (in blue).

In the cited work,\textsuperscript{20} the structures of the twelve more stable cations were calculated. The $1,7\text{H}$ cation, $8\text{cH}^+$ (in red), is the most stable both in the gas-phase and in water; the cation $6\text{cH}^+$ occupies the $8$\textsuperscript{th} place in order of stability. Here also there is a linear relationship between water and gas-phase stabilities: $E_{\text{rel water}} = (0.88 \pm 0.05) E_{\text{rel gas}}, n = 12, R^2 = 0.964$. Remember that $8\text{cH}^+$ is the structure found experimentally (Scheme 1 and section 3.3). The different structures of $3\text{H}^+$ and $8\text{cH}^+$ prevent a comparison between the basicity of indazoles $3$ and that of $1\text{H}$-benzo[de]cinnolines $1$. 

Figure 6. Protonation and deprotonation of benzo[de]cinnoline 6c compared with indazole 3.

B3LYP/6-31G(d,p) calculations were carried out on some of the cations of compound 38, Figure 7.13 The presence of the fourth ring in 1-ethyl-3-methyl-1H-indeno[6,7,1-def]cinnoline (38) modifies the preferred protonation site that now took place at carbon C6 (red).

Figure 7. Four possible cations resulting of the protonation 1-ethyl-3-methyl-1H-indeno[6,7,1-def]cinnoline (38).

Here again protonation on N2 leading to 38H+-H2 (blue) is highly disfavored. The structure of cation 38H+-H6 was established by 1H NMR using the spectra in CF3CO2H and CF3CO2D.13

3.3. Reactivity

3.3.1. On nitrogen atoms. Besides protonation (Section 3.2), we have reported in Scheme 1 an example of N-methylation, Scheme1(a), and two others of protonation, Scheme 1(b). According to Lacy et al.,6 protonation of 6a and 6c does not afford the cations 6aH+ and 6cH+ but structures protonated at C7, 8aH+ and 8cH+, based on the 1H NMR spectrum in CF3CO2H (Figure 8). Dorofeenko et al. demonstrated using 1H NMR in CF3CO2H that 6-methoxy-1H-benzo[de]cinnoline 13 and its N-methyl derivative protonate on C7.21
Figure 8. Results of the protonation of benzo[de]cinnolines 6c and 6a.

3.3.2. On carbon atoms. 3.3.2.1. Alkylation. Alkylation of 3-methyl-6,7-dihydro-1H-indeno[6,7,1-def]cinnoline (10) with methyl and propyl iodides as well as with benzyl chloride in alkaline medium leads to the formation of the corresponding both N-substituted (11, 39, 40) and 9-substituted cinnoline derivatives (41, 42) and also to the dimerization product (43) of the initial compound that corresponds to the formation of a N1-C9 bond (Scheme 3).

IR and $^1$H NMR spectra were used to establish the structures; remember that protonation takes place at C7 while the alkylation occurs at C9.

Scheme 3. Alkylation of 3-methyl-6,7-dihydro-1H-indeno[6,7,1-def]cinnolines.

3.3.2.2. Oxidation. The oxidation of 11 with chloranil affords the dehydro compound 1,3-dimethyl-1H-indeno[6,7,1-def]cinnoline (44) together with the dimer 43; similarly compound 45 was obtained from 12 (Figure 9). These compounds were characterized by mass spectrometry and by $^1$H NMR, in particular using 2D spectra (COSY). The reaction was extended to other 6,7-dihydro-1H-indeno[6,7,1-def]cinnoline where several dimers were isolated.

Figure 9. Structures of the oxidation products.

3.3.2.3. Nitration. Benzo[de]cinnolines could be dissected into aniline or better 1-naphthylamine and a pyridine, 46 (Figure 10); the pyridine suppressed the electrophilic aromatic substitution while aniline is nitrated in neutral conditions at ortho and para positions. 1-Naphthylamine is nitrated in position 4 (para). Isoquinoline is nitrated in positions 5 and 8. This oversimplified model suggests that the nitration of benzo[de]cinnolines should occur predominantly at positions 7 and 9 and then 4. In the experimental
results reported below in Scheme 4 all the starting benzo[de]cinnolines have the position 6 protected. Positions 4, 5 and 8 will never be attacked by electrophilic reagents in the absence of donor substituents in position 6 or 7.

![Chemical Structures](image)

**Figure 10.** The reactivity of benzo[de]cinnolines towards electrophiles.

Three papers by the Mezeritskii group report nitration experiments; the first paper results are summarized in Scheme 4 where dinitro (51-54) and trinitro (55-58) derivatives were isolated.²⁸

![Scheme 4](image)

**Scheme 4.** Nitration of 6-methoxy-3-methyl-1H-benzo[de]cinnolines.

The second paper²⁹ is much richer in results (Scheme 5) because nitration (61-64) competes with the oxidation of the C6C7 bond (38, 44, 63 and 64) and with the dimerization of the compound 10 to afford 43 (Scheme 5).

The last paper of the Mezeritskii group,³⁰ besides Schemes 6 and 7 results it reports theoretical calculations (Section 7). Starting from 59, five compounds are formed, 65 (oxidation and mononitration), 66 (loss of the acyl group and mononitration), 67 (loss of the acyl group and dinitration), 68 (dinitration) and 69 (loss of the acyl group and dinitration). The dihydro derivative 69 arises from the electrophilic addition of nitric acid to a double bond of 65 (Scheme 6).
Scheme 5. Nitration of 3-methyl-6,7-dihydro-1H-indeno[6,7,1-def]cinnolines.

Scheme 6. Nitration of 1-acetyl-3-methyl-6,7-dihydro-1H-indeno[6,7,1-def]cinnolines.

The results summarized in Scheme 7 are an extension to molecules having either H or different groups on N1 instead of an acetyl group, R = H (10), Me (11), Et (12), Pr (39), Bn (40) and Ph (70). Depending
on the nature of R, different structures were isolated: mononitrated 71 and 72; dinitrated 63, 64, 73, 74 and 75; and the corresponding dihydro derivatives 69-80. In the presence of methanol 81 was isolated.

Scheme 7. Nitration of 3-methyl-6,7-dihydro-1H-indeno[6,7,1-def]cinnolines.

The structure of 80 was first deduced from its $^1$H NMR spectrum and afterwards definitely established by X-ray crystallography (Figure 11). The structure has not been deposited in the CSD.$^{31}$

Figure 11. Structure of compound 80 adapted from reference.$^{39}$

3.3.2.4. Acylation. Similar in importance to the precedent studies about nitration are the acylation ones with the added complexity that there are several acyl groups, formyl, acetyl and trifluoroacetyl. The studies started with the formylation by means of the Vilsmeier-Haack reaction.$^{13}$ Scheme 8 shows that the reaction takes place at position 6 of 1-substituted-3-methyl-1H-indeno[6,7,1-def]cinnolines 44 and 38 to yield 6-formyl derivatives 82 and 83, in the same position than nitration, see compound 60, Scheme 5.

When position 1 is unsubstituted (N1H) acylation occurs in that position, Scheme 9; in that way 1-acyl derivatives 50, 59, 84 and 85 were prepared.


Scheme 10. Reaction of compounds 10 and 13 with trifluoroacetic anhydride.
The most extensive studies by Mezheritskii et al. concern the trifluoroacetylation. In the first paper, Scheme 10, besides N-COCF₃ derivatives, 86 and 87, they report C-COCF₃ derivatives, presenting a strong hydrogen bond, 88 and 89, and a dimer 90, 6,6’-dimethoxy-3,3’-dimethyl-1’H-1,9’-bibenzo[de]cinnoline, similar to dimer 43. A further study, Scheme 11, reports the synthesis of 91, 1,1’-(1-ethyl-6-methoxy-3-methyl-1H-benzo[de]cinnoline-7,9-diyl)bis(2,2,2-trifluoroethan-1-one), the X-ray structure of which, Cambridge Structural Database Refcode YEBHOF was determined, see Figure 12.

Scheme 11. Synthesis of 1,1’-(1-ethyl-6-methoxy-3-methyl-1H-benzo[de]cinnoline-7,9-diyl)bis(2,2,2-trifluoroethan-1-one) (91).

A last paper is summarized in Scheme 12, where the results of trifluoroacetylation of the most studied series (6-methoxy and that 6,7-etheno) afforded a large collection of mono and ditrifluoroacetylated compounds from 92 to 100. The X-ray structure of one of them 99, Cambridge Structural Database Refcode XOTJUO was determined, see Figure 12.

Scheme 12. Further examples of trifluoroacetylation.

4 Spectroscopy

4.1. UV and visible spectroscopies
Table 2 reports UV data of simple compounds.
Table 2. \( \lambda_{\text{max}} \) (nm) in EtOH (sh, shoulder)

<table>
<thead>
<tr>
<th>Compound</th>
<th>6a(^5)</th>
<th>6b(^5)</th>
<th>6c(^6)</th>
<th>7a(^5)</th>
<th>7b(^5)</th>
<th>8cH(^+) (^6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \lambda_{\text{max}} ) (nm)</td>
<td>332, 348, 349, 430</td>
<td>(sh), 341, 348, 365, 348, 427, 416</td>
<td>5 ( \lambda_{\text{max}} ) (nm)</td>
<td>230, 260, 332, 348, 416</td>
<td>238, 260, 349, 430</td>
<td>262, 330, 348, 365, 410, 434</td>
</tr>
</tbody>
</table>

Chenoweth \textit{et al.}\(^14\) reported that dibenzo[\textit{de,g}]cinnolines (Scheme 2) exhibit interesting photophysical properties. Dibenzo[\textit{de,g}]cinnolines \textit{21}, \textit{23} and \textit{28} are emissive in the solid state and in solution when irradiated at 365 nm. Live-cell imaging of HeLa cells in the presence of protonated \textit{24} upon excitation at 405 nm using confocal microscopy shows that intracellular vesicles can be selectively stained.

4.2. NMR spectroscopy

Regarding NMR spectroscopy, most publications report \(^1\)H and \(^{13}\)C data but only as peak lists without assignment of the signals. For simple molecules, experimental \(^1\)H NMR data, chemical shifts and coupling constants, are reported in Table 3.

Table 3. \(^1\)H NMR chemical shifts (\( \delta \), ppm) and \(^1\)H-\(^1\)H coupling constants (Hz)

<table>
<thead>
<tr>
<th>Solv.</th>
<th>6c</th>
<th>6a(^*)</th>
<th>6b</th>
<th>7a</th>
<th>8cH(^+)</th>
<th>8aH(^+)</th>
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<tr>
<td>R(^1)</td>
<td>H</td>
<td>7.0-7.3</td>
<td>7.0-7.3</td>
<td>7.0-7.3</td>
<td>7.0-7.3</td>
<td>7.0-7.3</td>
</tr>
<tr>
<td>R(^3)</td>
<td>H</td>
<td>7.12</td>
<td>7.38, ( J_{\text{AS}} = 7.5 )</td>
<td>7.31, ( J_{\text{AS}} = 7.6 )</td>
<td>7.1-7.4</td>
<td>8.3</td>
</tr>
<tr>
<td>R(^3)</td>
<td>H</td>
<td>7.12</td>
<td>7.12</td>
<td>7.1-7.4</td>
<td>8.3</td>
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<td>1</td>
<td>8.16</td>
<td>8.28 (br)</td>
<td>8.26 (br)</td>
<td>3.40</td>
<td>N.o.</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>7.0-7.3</td>
<td>2.16</td>
<td>**</td>
<td>2.15</td>
<td>9.4</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>7.0-7.3</td>
<td>7.38, ( J_{\text{AS}} = 7.5 )</td>
<td>7.31, ( J_{\text{AS}} = 7.6 )</td>
<td>7.1-7.4</td>
<td>8.3</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>7.0-7.3</td>
<td>7.12</td>
<td>**</td>
<td>2.15</td>
<td>9.4</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>6.8, ( J = 1.5, 9.0 )</td>
<td>6.87, ( J_{\text{AS}} = 8.1 )</td>
<td>6.92, ( J_{\text{AS}} = 8.2 )</td>
<td>6.90 (( J = 8 ))</td>
<td>8.3</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>6.6, ( J = 2.5, 6.0 )</td>
<td>6.65, ( J_{\text{AS}} = 7.3 )</td>
<td>6.74, ( J_{\text{AS}} = 7.3 )</td>
<td>6.70 (( J = 7 ))</td>
<td>4.5 (br)</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>7.0-7.3</td>
<td>7.12</td>
<td>7.12</td>
<td>7.1-7.4</td>
<td>7.6, ( J_{\text{AS}} = 10.0, J_{78} = 4.0 )</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>6.1, ( J = 1.0, 7.0 )</td>
<td>6.21, ( J_{\text{AS}} = 7.0 )</td>
<td>6.23, ( J_{\text{AS}} = 7.0 )</td>
<td>6.05 (( J = 7 ))</td>
<td>7.3, ( J_{78} = 1.0 )</td>
<td></td>
</tr>
</tbody>
</table>

\* Also reported in ref.\(^5\) but probably with a lower field apparatus (not given) than that used more recently (200 MHz).\(^7\)

** 3-Phenyl signals: 7.45 (3H, \( m-H, p-H \)), 7.56 (2H, o-H, \( J = 6.9 \)).

These values will be compared with the calculated chemical shifts (Section 6). Like most recent papers, the experimental part contains \(^1\)H NMR \(^9,13,30,31,37-39,44\) and \(^{13}\)C NMR \(^11,37,43\) data. \(^{15}\)N NMR data are however still scarce\(^37\) (see Section 7).
5. Mass Spectrometry

In most cases, only the molecular ion is given, in some others just a list of fragments\textsuperscript{13,37} while in other cases, the fragmentation mechanisms are discussed.\textsuperscript{10-12}

6. X-Ray Crystallography

A search in the Cambridge Structural Database\textsuperscript{40} affords seven X-ray structures having the skeleton of 1\textit{H}-benzo[de]cinnolines. In Figure 12 we have shown all of them with the correlation of the compound numbers with the Cambridge Structural Database Refcodes.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{Figure_12}
\caption{X-ray structures of 1\textit{H}-benzo[de]cinnolines and 1\textit{H}-benzo[de]cinnolones.}
\end{figure}

Several of these structures were published without comments: \textsuperscript{83, 36, 37 and 20}. The dimer \textsuperscript{43} has bond lengths and bond angles close to standard values; the two halves are planar and near orthogonal (86.0\textdegree), and form a dimer through two N–H⋯N hydrogen bonds.\textsuperscript{11} In compound \textsuperscript{99}, the acenaphthene skeleton is almost planar whereas the heterocycle is somewhat distorted due to the proximity of the phenyl and the COCF\textsubscript{3} moiety.\textsuperscript{44} The tricyclic system of \textsuperscript{91} approaches planar configuration but the N1-ethyl and C9-trifluoroactyl groups deviate from the corresponding ring planes.\textsuperscript{43}
7. Theoretical Calculations

Table 4 reports the calculated chemical shifts of the simplest benzo[de]cinnolines, R = H or CH₃. The GIAO/B3LYP/6-311++G(d,p) calculations afford absolute shieldings (σ, ppm) that were transformed into chemical shifts (δ, ppm) using empirical equations that we have already established from a large set of compounds.³⁶,³⁷

Table 4. GIAO/B3LYP/6-311++G(d,p) calculated NMR chemical shifts (δ, ppm)

<table>
<thead>
<tr>
<th></th>
<th>6c</th>
<th>6a</th>
<th>6b</th>
<th>7a</th>
<th>8cH⁺</th>
<th>8aH⁺</th>
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<tr>
<td>R¹</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>CH₃</td>
<td>H</td>
<td>H</td>
</tr>
<tr>
<td>R³</td>
<td>H</td>
<td>CH₃</td>
<td>C₆H₅</td>
<td>CH₃</td>
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<td>CH₃</td>
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<td>H1</td>
<td>7.26</td>
<td>7.38</td>
<td>7.50</td>
<td>3.34 (Me)</td>
<td>10.14</td>
<td>9.99</td>
</tr>
<tr>
<td>H3</td>
<td>7.06</td>
<td>2.03 (Me)</td>
<td>(Ph)*</td>
<td>2.08 (Me)</td>
<td>9.06</td>
<td>3.02 (Me)</td>
</tr>
<tr>
<td>H4</td>
<td>6.37</td>
<td>6.82</td>
<td>6.77</td>
<td>6.54</td>
<td>8.18</td>
<td>8.24</td>
</tr>
<tr>
<td>H5</td>
<td>7.05</td>
<td>7.14</td>
<td>7.04</td>
<td>7.21</td>
<td>8.52</td>
<td>8.50</td>
</tr>
<tr>
<td>H6</td>
<td>7.09</td>
<td>7.20</td>
<td>7.17</td>
<td>7.27</td>
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<tr>
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* 3-Phenyl group: Ho = 7.61, Hm = 7.40, Hp = 7.35; Ci = 138.6, Co = 128.4, Cm = 127.9, Cp = 128.0.

The experimental ¹H NMR chemical shifts, δ ppm, of Table 3 correlate quite well with the calculated ones (Table 4): δ Exp. = (0.21±0.16) + (0.98±0.02) δ Calc. + (0.80±0.15) NH, n = 48, R² = 0.976. The three NH protons need a correction of 0.80 ppm due to specific solvent effects.
Concerning $^{15}$N-shifts, the only experimental data are those of reference$^{37}$ – they are consistent with the calculated values for 7a assuming that the reported data use ammonia as reference compound; we have transformed them to nitromethane reference by subtracting 380.2 ppm (Figure 13).

![Figure 13. Calculated for 7a and experimental $^{15}$N chemical shifts of 49 and 53 ($\delta$, ppm). For the 7-nitro group of 53 there are two values in reference, one in the main text and the other in the experimental part.](image)

Pozharskii and Malysheva calculated with the Hückel approximation, HMO, the electronic properties of some derivatives including 1 and 2 in 1970.$^{38}$ Much later, in 2018, B3LYP/6-311++G(d,p) calculations were carried out on the complexes of HNO$_3$ hydrogen bonded (HB) to different positions of compound 12$^{39}$ (Figure 14). The minimum has a bifurcated HB to N1 and C3. There is no evidence that these calculations would be useful to discuss the positions of nitration.

![Figure 14. Structures of compounds 1, 2 and 12.](image)

Compound 1 together with other aza derivatives of phenalene, including perimidine 2, have been calculated with the (RO)B3LYP method, where RO stands for restricted open-shell, with the aim of designing stable radical molecular materials.$^{39}$

Finally, there are two papers by Tsoungas et al. in 2018 and 2021.$^{40,41}$ on the aromaticity of 1H-benzo[de]cinnolines and related heterocycles based on NICS calculations, compound 1 being the most aromatic.$^{43}$ In the cited work of Tsoungas et al.,$^{44}$ they analyzed the MEP to indicate that the reactivity of electrophiles towards 1 will occur at positions 3, 6 and 9, which is not the case.

8. Biological Properties

Actually there are no medicinal papers reporting biological properties of 1H-benzo[de]cinnolines. The only publication is due to Baell and Holloway, where a large series of substructures are included in the Supporting Information$^{42}$ Amongst these substructures, there is compound 1 with the code number 350 and the name naphth_a.mino_C(2). Since cinnolines belong to a class of heterocyclic compounds with rich pharmaceutical properties,$^{43}$ those of 1H-benzo[de]cinnolines deserve to be explored.
9. Conclusions

The chemistry of 1H-benzo[de]cinnolines, 6H-dibenzo[de,g]cinnolines and 1H-indeno[6,7,1-def]cinnolines is at the present moment sufficiently reduced to be covered in its integrity. The results reported here show that these compounds are easily prepared and sufficiently stable to allow a number of reactions. However, compared to perimidines many reactions have never been tested offering new chemical research avenues. Also, their physical and biological properties are clearly underdeveloped. For instance, almost nothing is known about the properties related to excited states, on their coordination to metals, and on their biological properties. May this review hopefully increase interest in these molecules, important cornerstones in the building of heterocyclic chemistry.

10. Acknowledgments

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Data availability

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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Abbreviations

B3LYP Becke 3-parameter Lee Yang Parr
GIAO Gauge Invariant Atomic Orbital
HB Hydrogen Bond
MEP Molecular Electrostatic Potential
NICS Nucleus Independent Chemical Shifts
PCM Polarizable Continuum Model

References

4. Certain data included herein are derived from Clarivate Web of Science. © Copyright Clarivate 2022. All rights reserved.
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