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Review

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1*H*-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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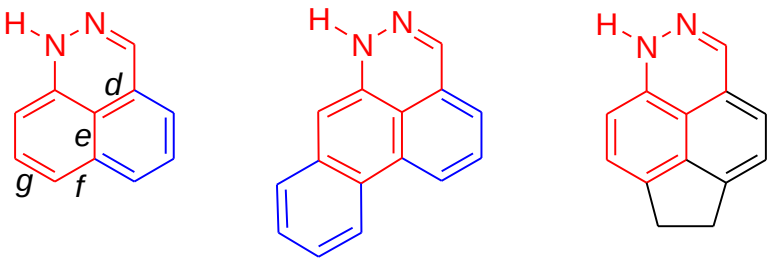
Abstract

1*H*-Benzo[*de*]cinnolines, 6*H*-dibenzo[*de,g*]cinnolines and 1*H*-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: 1*H*-Benzo[*de*]cinnolines, 1*H*-indeno[6,7,1-*def*]cinnolines, perimidines, protonation, tautomerism

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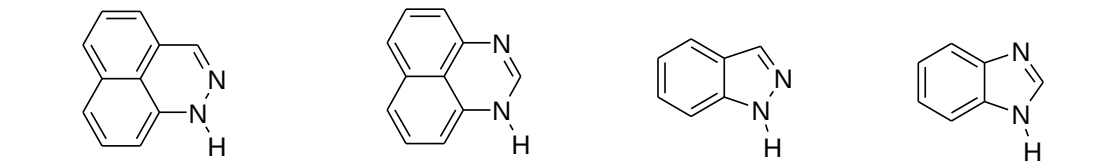
1. Introduction

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



1 1*H*-benzo[*de*]cinnoline **2** 1*H*-perimidine **3** 1*H*-Indazole **4** 1*H*-Benzimidazole

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 diazaphenalenes, peridazines, etc. The main contribution to both benzo[*de*]cinnolines and perimidines came from two groups of the Southern Federal University (Rostov-on-

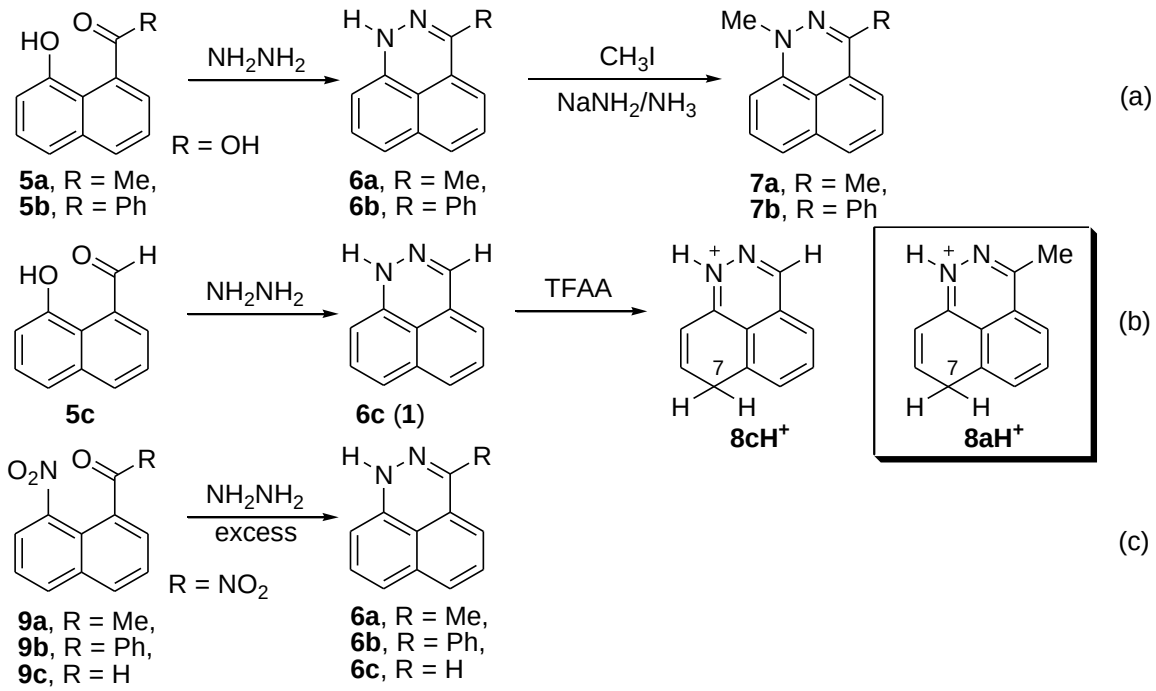
Don, Russia); Pozharskii's group in the field of perimidines **2**, 105 references out of 387 are from his group in our 2020 review;[1] analogously, Mezheritskii group in the field of benzo[*de*]cinnolines **1**, 15 references out of 51 are from his group in the present review.

Table 1. Number of references cited in the literature

	Web of Science	ScienceDirect
Benzimidazoles **4**	38,906	31,841
Indazoles **3**	5,530	5,223
Ratio **4/3**	7.0	6.1
Perimidines **2**	211	287
Benzo[*de*]cinnolines **1**	3	4
Ratio **2/1**	70.3	71.8

2. Synthetic Methodologies

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



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

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

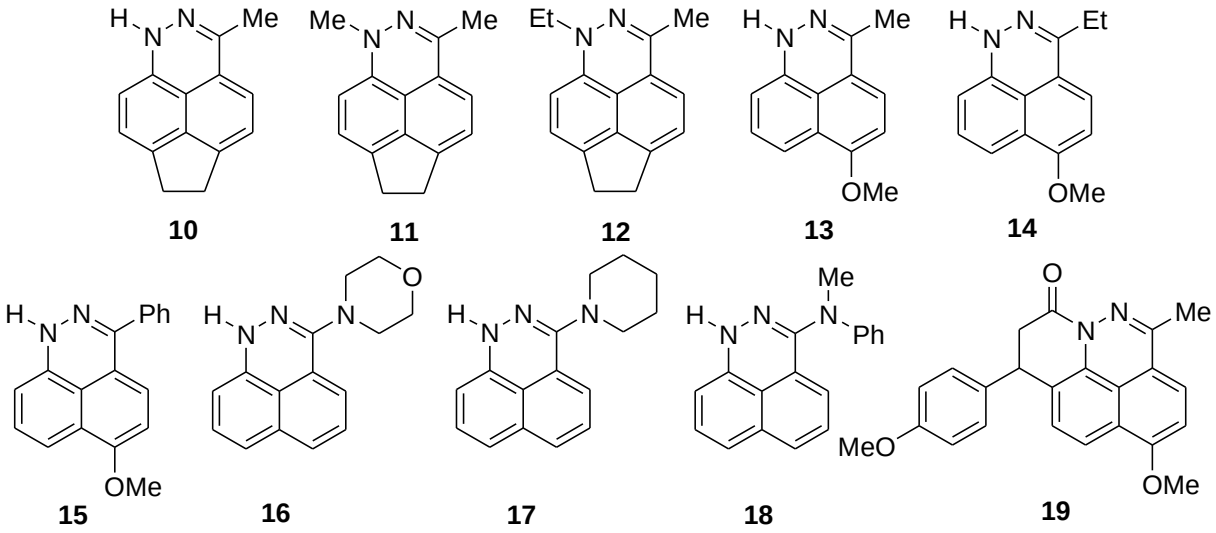
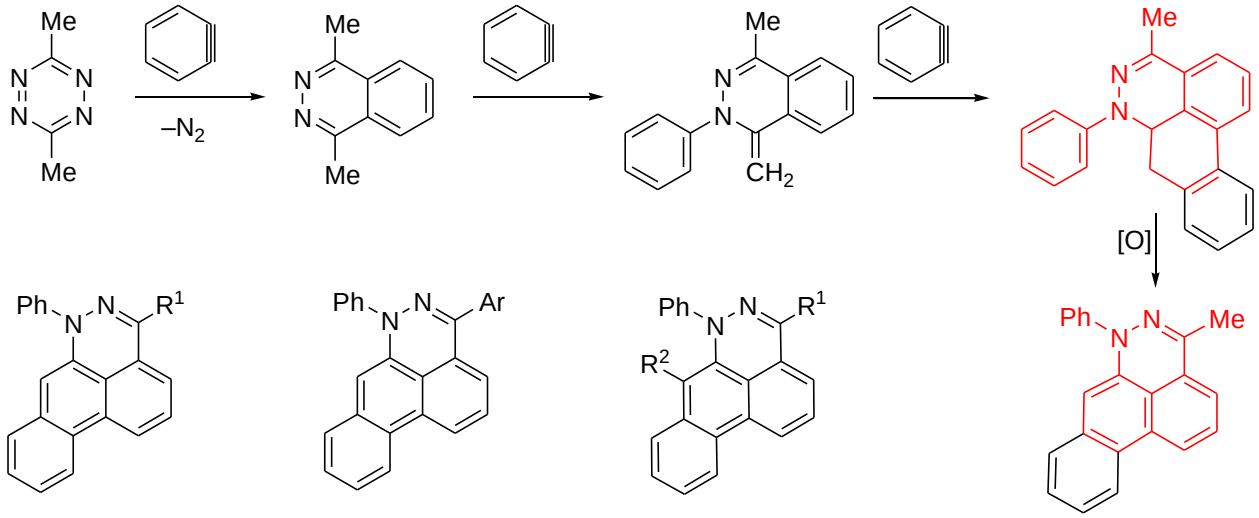


Figure 2. 1*H*-benzo[*de*]cinnolines prepared according to the method described in 1(a).

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-6*H*-dibenzo[*de,g*]cinnolin[10] They have prepared a large set of compounds, **20**-**32**, and some dimethyl derivatives starting from 4,5-dimethyl-*o*-benzyne (Scheme 2).



21, R^1 = C_9H_{19}
22, R^1 = adamantyl

23, Ar = phenyl
24, Ar = *p*-Br-phenyl
25, Ar = *o*-F-phenyl
26, Ar = OCH_2OCH_3
27, Ar = CH_2NHCO_2tBu
28, Ar = 2-thienyl
29, Ar = 2-pyridyl

30, R^1 = C_2H_5, R^2 = CH_3
31, R^1 = R^2 = C_9H_{19}
32, R^1 = phenyl, R^2 = CH_3

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

3. Reactivity of 1*H*-Benzo[*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, 1*H* and 2*H*, are of different energy.[12,13]

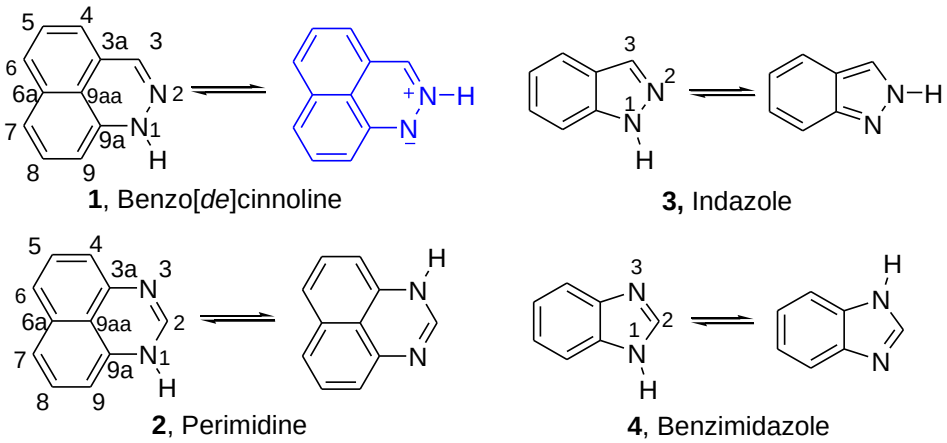


Figure 3. The prototropic relationships in compounds **1** to **4**.

In *N*-unsubstituted benzo[*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 1*H*-benzo[*de*]cinnoline have also CH tautomers that are much less stable because the aromaticity is totally or partially lost. A recent work[14] where theoretical B3LYP/6-311++G(d,p) calculations[15,16] were carried out using the Gaussian 16 set of programs[17] including general solvent effects (PCM method)[18] resulted in the data depicted in Figure 4.

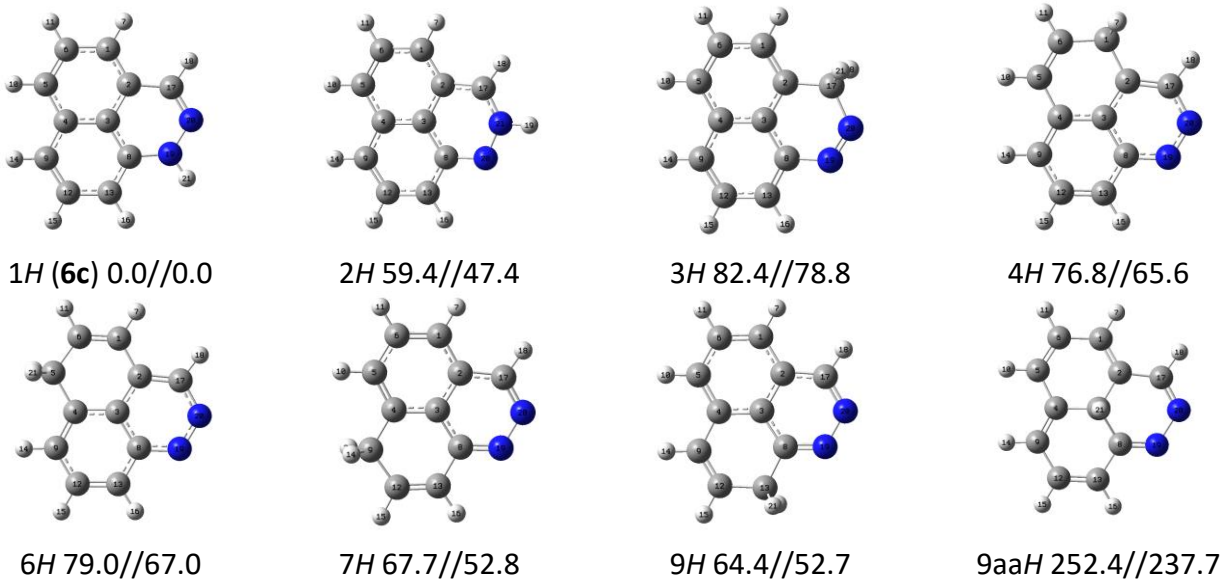


Figure 4. Relative energies (E_{rel} in kJ·mol^{-1}) of the eight tautomers of benzo[*de*]cinnoline **6c** (**1**) in the gas-phase//in water.

1. Water *vs*. gas: E_{rel} water = –(6.7±2.7) + (0.96±0.02) E_{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_{rel} gas values.

2. The zwitterion 2*H* although highly unstable compared with the 1*H* tautomer is still more stable than any CH tautomer.

3. The two most stable CH tautomers are 7*H* and 9*H*. The 9aa*H*-tautomer is very unstable due to the destruction of the aromaticity of two benzene rings.

3.1.2. Functional tautomerism. Similarly to indazolinones[19-21] 3-hydroxy-1*H*-benzo[*de*]cinnolines can present functional tautomerism between an oxo-tautomer **33** (1-methyl-1,2-dihydro-3*H*-benzo[*de*] cinnolin-3-one) and the corresponding hydroxy-tautomer **34** (1-methyl-1*H*-benzo[*de*]cinnolin-3-ol); however, the only reported compounds are analogs of 1,2-dimethyl-1,2-dihydro-3*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**, HIPPIT, and **37**, HIPPOL, have been determined[19,20] (Figure 5).

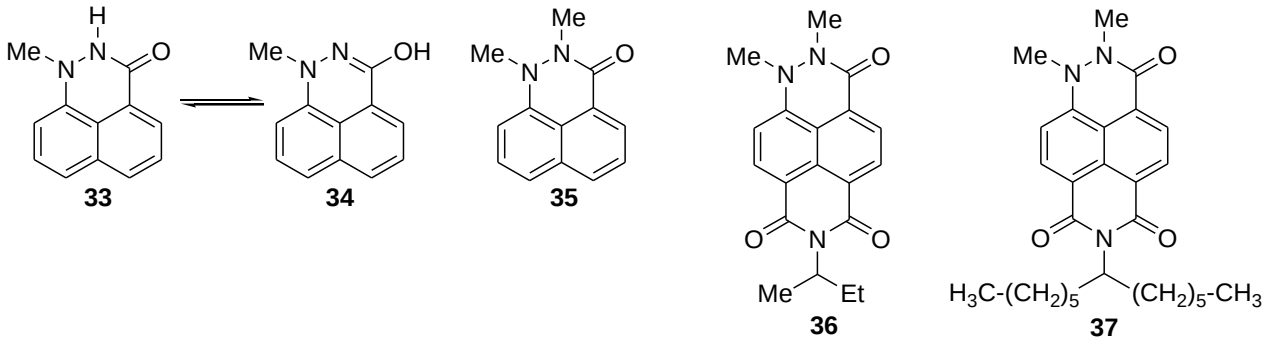


Figure 5. The tautomerism of 1*H*-benzo[*de*]cinnolones.

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 **6c** is the C-protonated **8cH$^+$** (in red) and not the N2-protonated **6cH$^+$** (in blue).

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

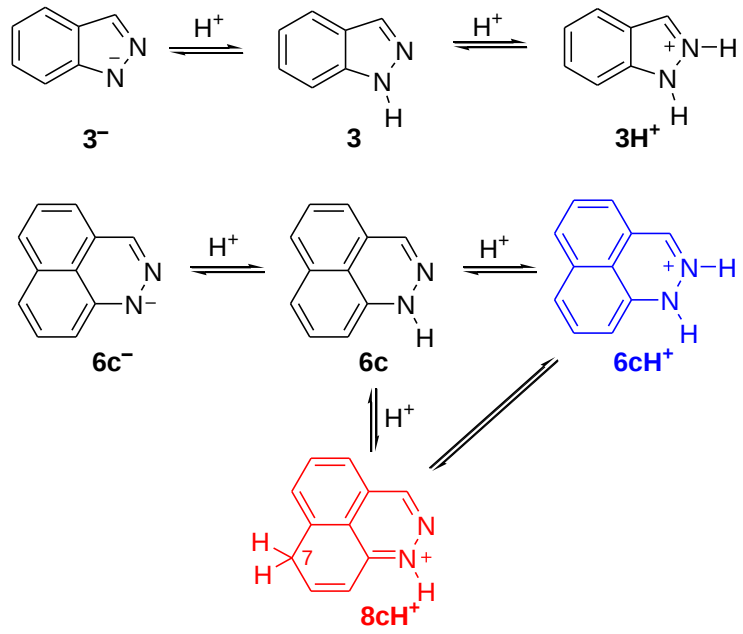


Figure 6. Protonation and deprotonation of benzo[*de*]cinnoline **6c** compared with indazole **3**.

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-1*H*-indeno[6,7,1-*def*]cinnoline (**38**) modifies the preferred protonation site that now took place at carbon C6 (red).

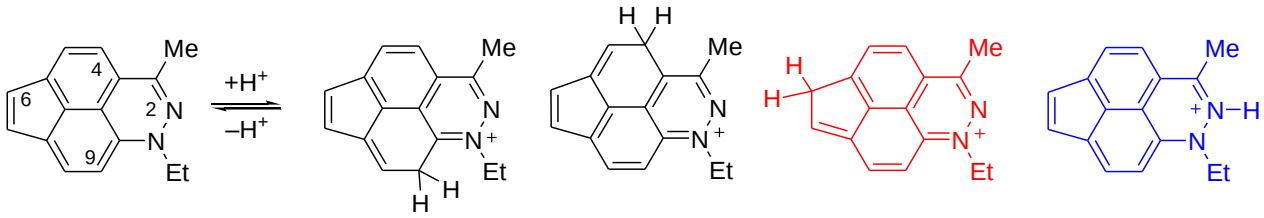
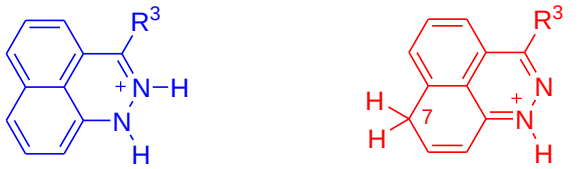


Figure 7. Four possible cations resulting of the protonation 1-ethyl-3-methyl-1*H*-indeno[6,7,1-*def*]cinnoline (**38**).

Here again protonation on N2 leading to **38H**$^+$-H2 (blue) is highly disfavored. The structure of cation **38H**$^+$-H6 was established by ^{1}H NMR using the spectra in CF_3CO_2H and CF_3CO_2D.[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 ^{1}H NMR spectrum in CF_3CO_2H (Figure 8). Dorofeenko *et al*. demonstrated using ^{1}H NMR in CF_3CO_2H that 6-methoxy-1*H*-benzo[*de*]cinnoline **13** and its *N*-methyl derivative protonate on C7.[21]

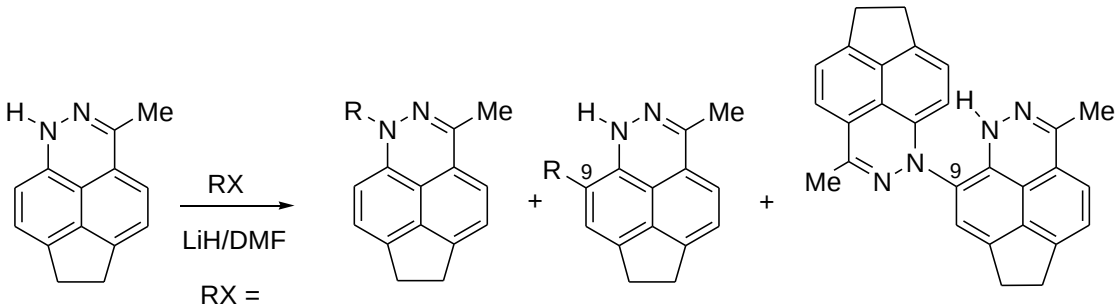


6cH$^+$, R^3 = H
6aH$^+$, R^3 = Me

8cH$^+$, R = H
8aH$^+$, R = Me

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-1*H*-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).[22] 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.



10

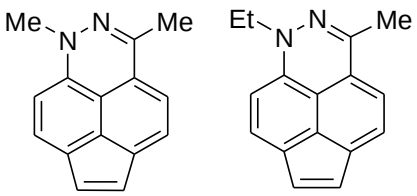
a, R = Me, **11**
b, R = Pr, **39**
c, R = Bn, **40**

b, R = Pr, **41**
c, R = Bn, **42**

43

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

3.3.2.2. Oxidation. The oxidation of **11** with chloranil affords the dehydro compound 1,3-dimethyl-1*H*-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).[10] The reaction was extended to other 6,7-dihydro-1*H*-indeno[6,7,1-*def*]cinnoline where several dimers were isolated.[11]



44 **45**

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[23] while aniline is nitrated in neutral conditions at *ortho* and *para* positions.[24,25] 1-Naphthylamine is nitrated in position 4 (*para*).[26] Isoquinoline is nitrated in positions 5 and 8.[27] 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.

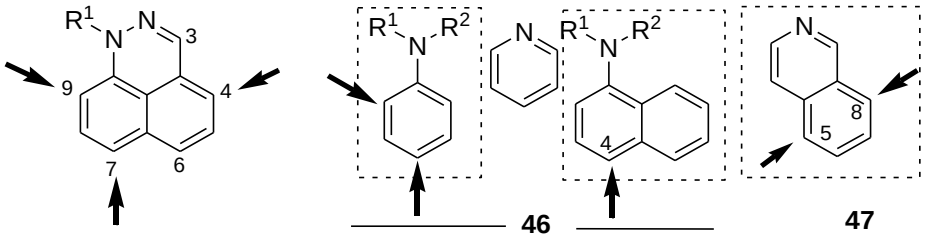
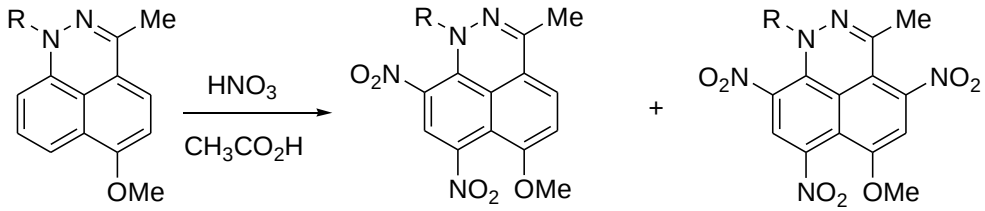


Figure 10. The reactivity of benzo[*de*]cinnolines towards electrophiles.

Three papers by the Mezheritskii 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]



13, R = H
48, R = Me
49, R = Et
50, R =COMe

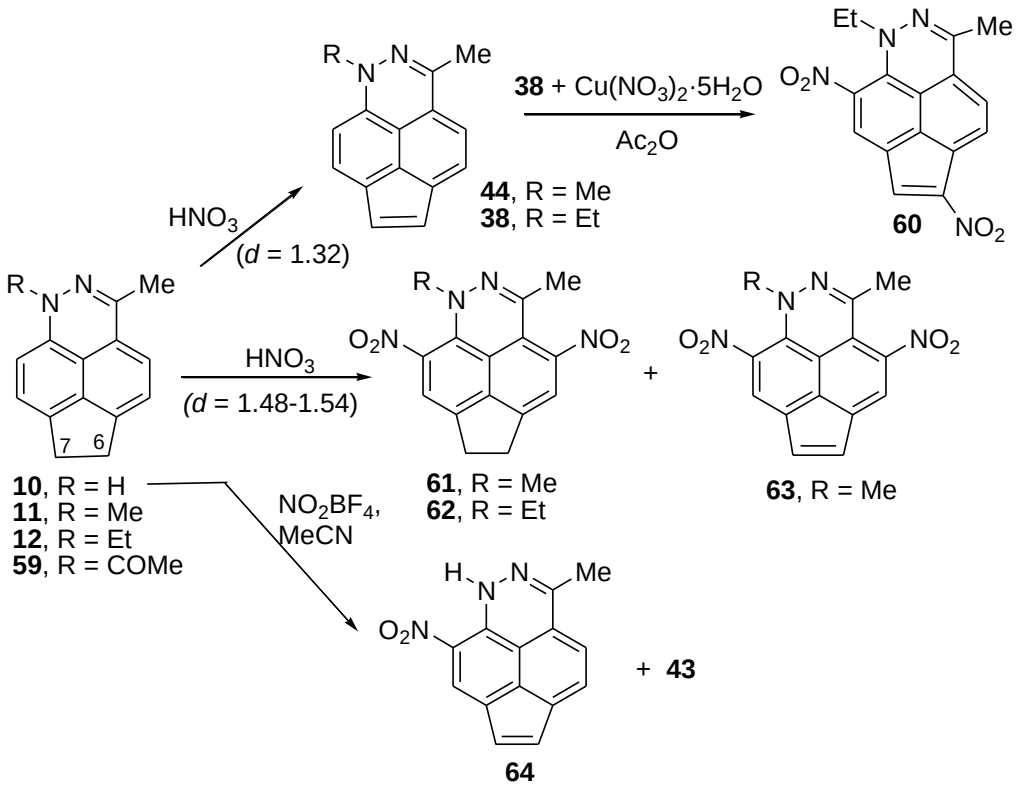
51, R = H
52, R = Me
53, R = Et
54, R = COMe

55, R = H
56, R = Me
57, R = Et
58, R = COMe

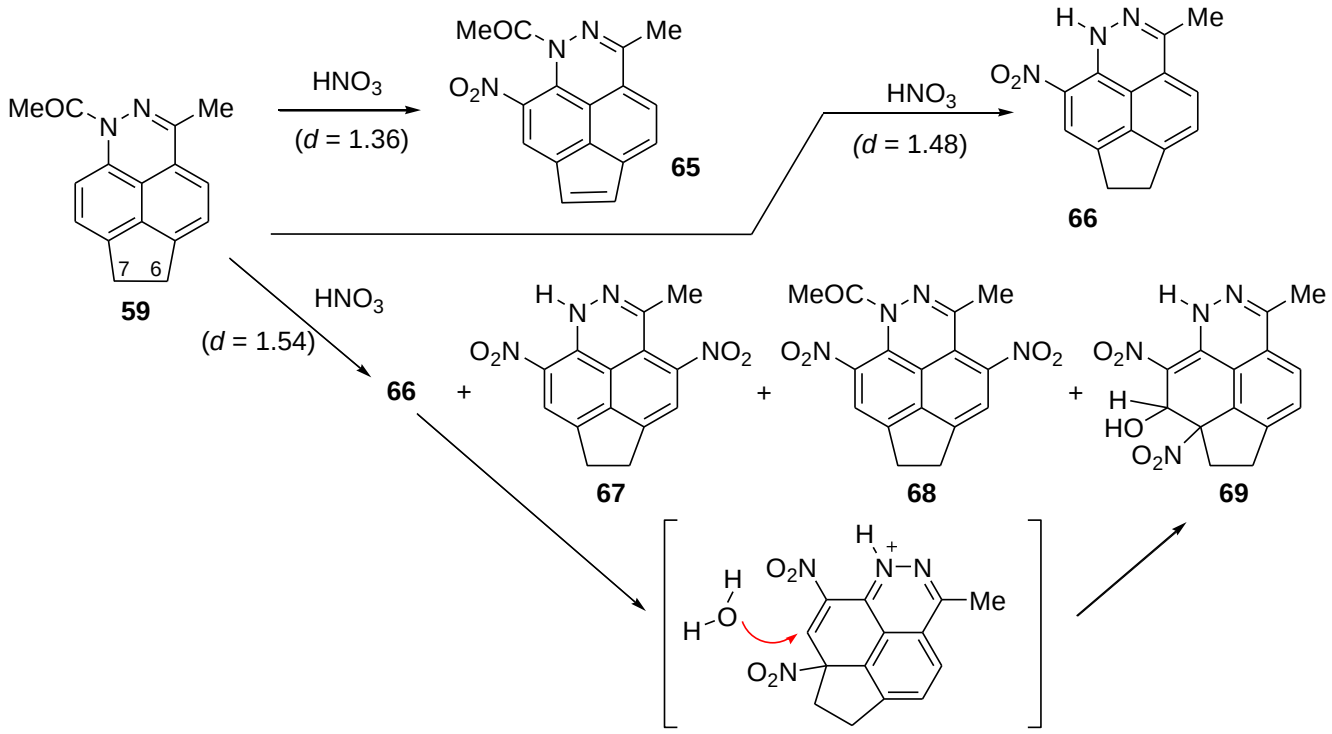
Scheme 4. Nitration of 6-methoxy-3-methyl-1*H*-benzo[*de*]cinnolines.

The second paper[29] 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 Mezheritskii 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).



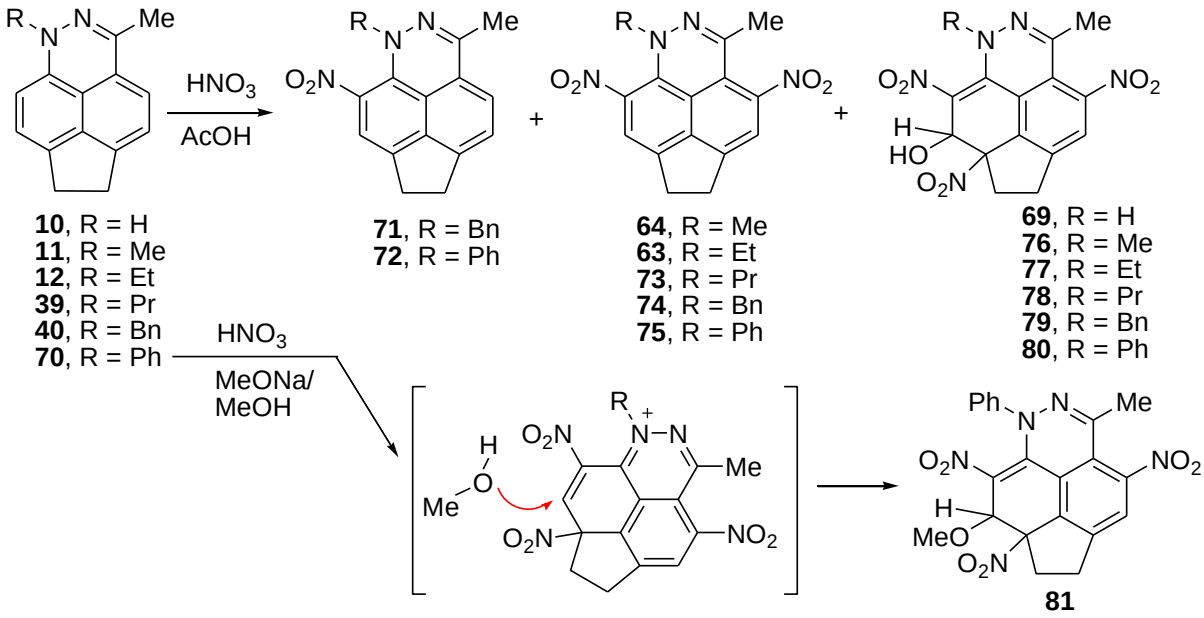
Scheme 5. Nitration of 3-methyl-6,7-dihydro-1*H*-indeno[6,7,1-*def*]cinnolines.



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

The results summarized in Scheme 7[39] 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-1*H*-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]

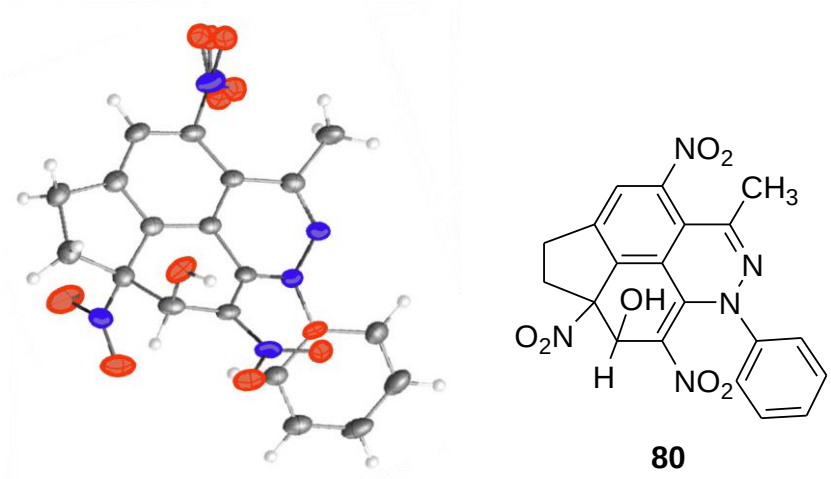
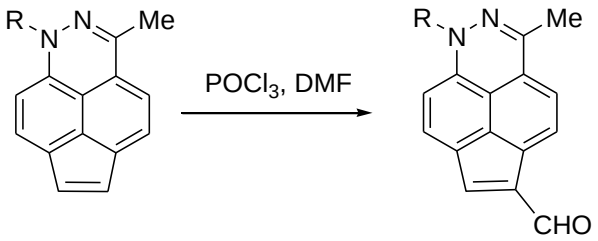


Figure 11. Structure of compound **80** adapted from reference.[39]

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-1*H*-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.

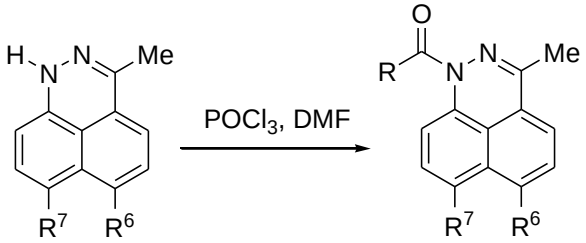


44, R = Me
38, R = Et

82, R = Me
83, R = Et

Scheme 8. Formylation of 1-ethyl-3-methyl-1*H*-indeno[6,7,1-*def*]cinnoline.

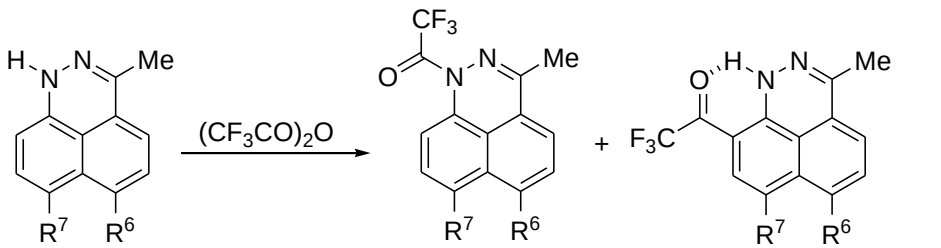
When position 1 is unsubstituted (N1H) acylation occurs in that position, Scheme 9;[32] in that way 1-acyl derivatives **50**, **59**, **84** and **85** were prepared.



10, $R^6R^7 = CH_2CH_2$
13, R^6 = OMe, R^7 = H

59, R = Me, $R^6R^7 = CH_2CH_2$
50, R = Me, R^6 = OMe, R^7 = H
84, R = Et, $R^6R^7 = CH_2CH_2$
85, R = Et, R^6 = OMe, R^7 = H

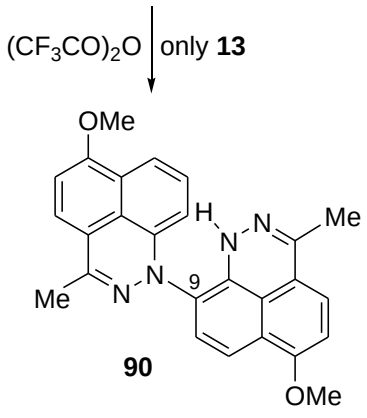
Scheme 9. Acetylation and propionylation of 1*H*-benzo[*de*]cinnolines and 1*H*-indeno[6,7,1-*def*]cinnolines.



10, $R^6R^7 = CH_2CH_2$
13, R^6 = OMe, R^7 = H

86, $R^6R^7 = CH_2CH_2$
87, R^6 = OMe, R^7 = H

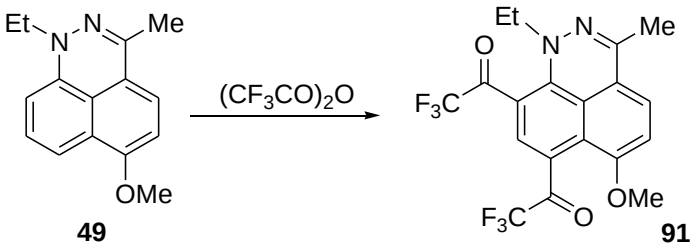
88, $R^6R^7 = CH_2CH_2$
89, R^6 = OMe, R^7 = H



90

Scheme 10. Reaction of compounds **10** and **13** with trifluoroacetic anhydride.

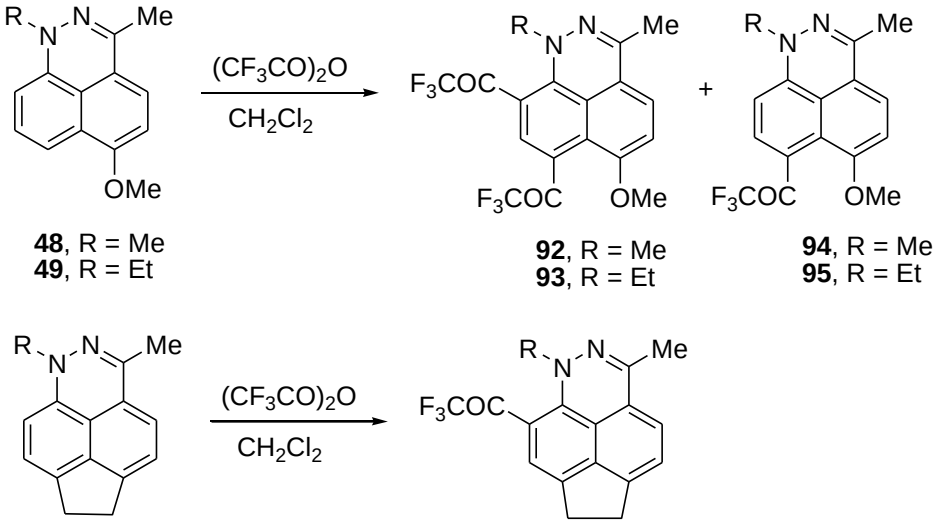
The most extensive studies by Mezheritskii *et al*. concern the trifluoroacetylation. In the first paper,[33] Scheme 10, besides N-$COCF_3$ derivatives, **86** and **87**, they report C-$COCF_3$ derivatives, presenting a strong hydrogen bond, **88** and **89**, and a dimer **90**, 6,6'-dimethoxy-3,3'-dimethyl-1'*H*-1,9'-bibenzo[*de*]cinnoline, similar to dimer **43**. A further study,[34] Scheme 11, reports the synthesis of **91**, 1,1'-(1-ethyl-6-methoxy-3-methyl-1*H*-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.



49 **91**

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

A last paper[35] 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.



48, R = Me
49, R = Et

92, R = Me
93, R = Et

94, R = Me
95, R = Et

11, R = Me
12, R = Et
39, R = Pr
70, R = Ph
40, R = Bn

96, R = Me
97, R = Et
98, R = Pr
99, R = Ph
100, R = Bn

Scheme 12. Further examples of trifluoroacetylation.

4 Spectroscopy

4.1. UV and visible spectroscopies

Table 2 reports UV data of simple compounds.

Table 2. λ_{max} (nm) in EtOH (sh, shoulder)

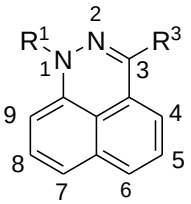
	6a[5]	**6b**[5]	**6c**[6]	**7a**[5]	**7b**[5]	**8cH$^+$** [6]
Compound λ_{max} (nm)	230, 260, 332, 348, 416	238, 260, 349, 430	261, 332 (sh), 341, 421, 441	262, 330, 348, 365, 410, 434	236, 260, 348, 427, 446	268, 343

Chenoweth *et al*.[14] reported that dibenzo[*de,g*]cinnolines (Scheme 2) exhibit interesting photophysical properties. Dibenzo[*de,g*]cinnolines **21**, **23** and **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 **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 (δ, ppm) and ^{1}H-^{1}H coupling constants (Hz)



	6c	**6a**[*]	**6b**	**7a**	**8cH$^+$**	**8aH$^+$**
Solv.	$CDCl_3$	$CDCl_3$	$CDCl_3$	$CDCl_3$	CF_3CO_2H	CF_3CO_2H
R^1	H	H	H	CH_3	H	H
R^3	H	CH_3	C_6H_5	CH_3	H	CH_3
Ref.	[6]	[7]	[7]	[5]	[6]	[6]
1	8.16	8.28 (br)	8.26 (br)	3.40	N.o.	N.o.
3	7.0-7.3	2.16	[**]	2.15	9.4	3.1
4	7.0-7.3	7.38, J_{45} = 7.5	7.31, J_{45} = 7.6	7.1-7.4	8.3	8.3
5	7.0-7.3	7.12	7.12	7.1-7.4	8.3	8.3
6	6.8, *J* = 1.5, 9.0	6.87, J_{56} = 8.1	6.92, J_{56} = 8.2	6.90 (*J* = 8)	8.3	8.3
7	6.6, *J* = 2.5, 6.0	6.65, J_{78} = 7.3	6.74, J_{78} = 7.3	6.70 (*J* = 7)	4.5 (br)	4.5 (br)
8	7.0-7.3	7.12	7.12	7.1-7.4	7.6, J_{89} = 10.0, J_{78} = 4.0	7.5, J_{89} = 10.0, J_{78} = 4.0
9	6.1, *J* = 1.0, 7.0	6.21, J_{89} = 7.0	6.23, J_{89} = 7.0	6.05 (*J* = 7)	7.3, J_{79} = 1.0	7.3

[*] 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 (d, 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[13,37] while in other cases, the fragmentation mechanisms are discussed.[10-12]

6. X-Ray Crystallography

A search in the Cambridge Structural Database[40] affords seven X-ray structures having the skeleton of 1*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.

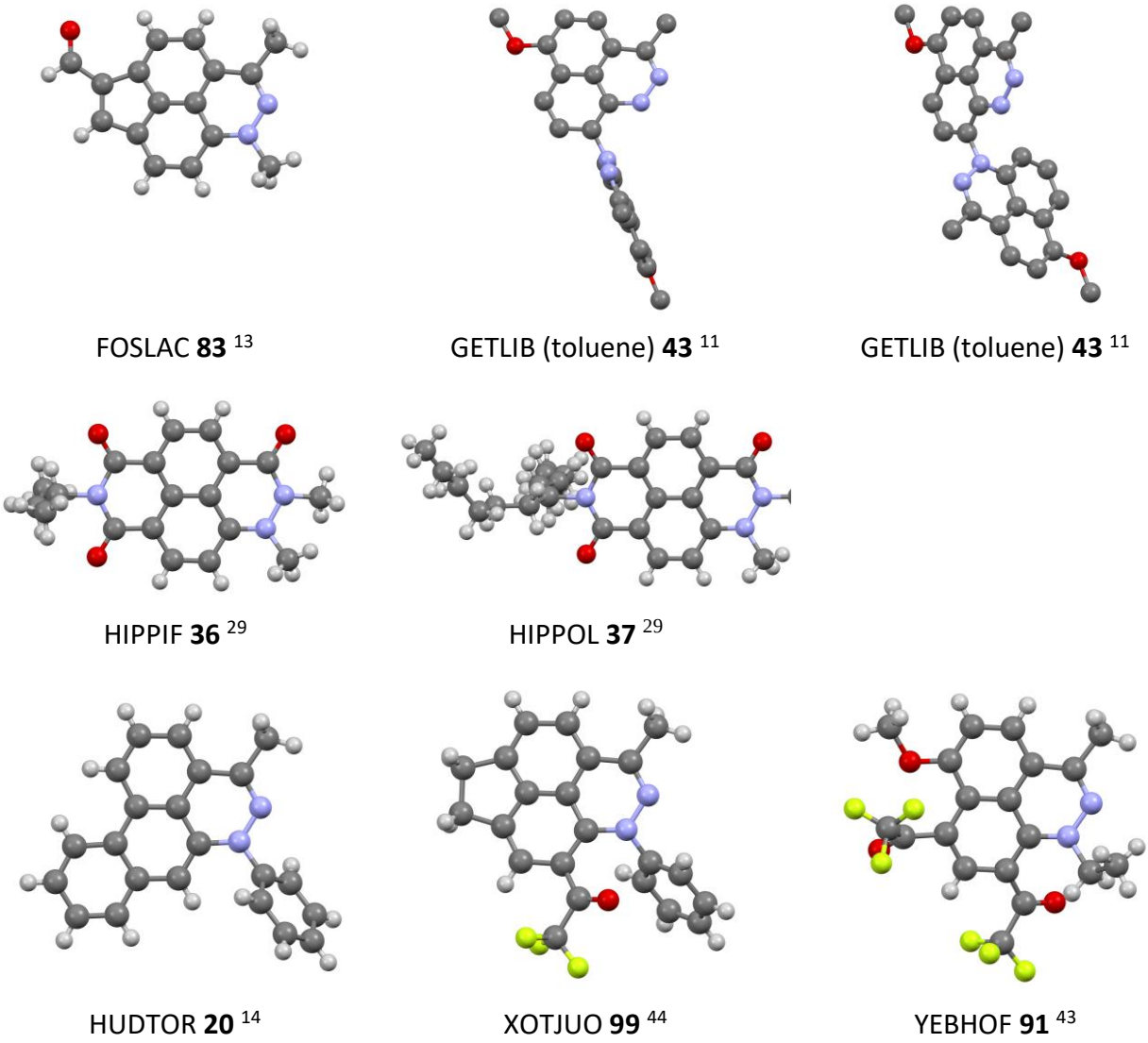


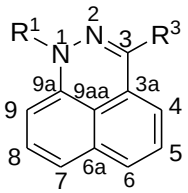
Figure 12. X-ray structures of 1*H*-benzo[*de*]cinnolines and 1*H*-benzo[*de*]cinnolones.

Several of these structures were published without comments: **83**, **36**, **37** and **20**. The dimer **43** has bond lengths and bond angles close to standard values; the two halves are planar and near orthogonal (86.0°), and form a dimer through two N–H···N hydrogen bonds.[11] In compound **99**, the acenaphthene skeleton is almost planar whereas the heterocycle is somewhat distorted due to the proximity of the phenyl and the $COCF_3$ moiety.[44] The tricyclic system of **91** approaches planar configuration but the *N*1-ethyl and C9-trifluoroactyl groups deviate from the corresponding ring planes.[43]

7. Theoretical Calculations

Table 4 reports the calculated chemical shifts of the simplest benzo[*de*]cinnolines, R = H or CH_3. 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)

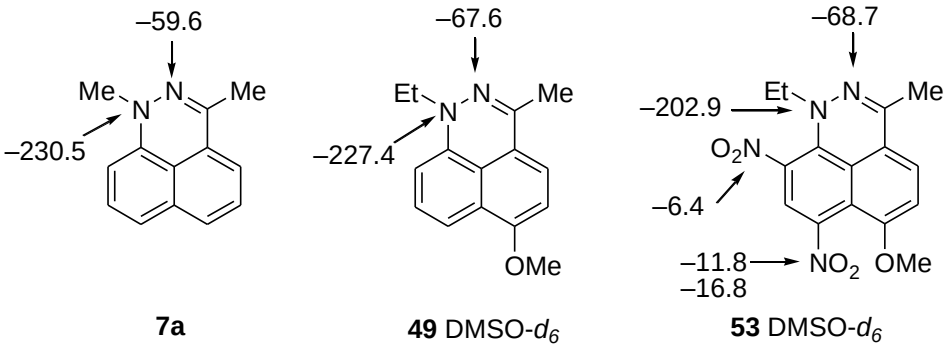


	6c	6a	6b	7a	8cH$^+$	8aH$^+$
R^1	H	H	H	CH_3	H	H
R^3	H	CH_3	C_6H_5	CH_3	H	CH_3
H1	7.26	7.38	7.50	3.34 (Me)	10.14	9.99
H3	7.06	2.03 (Me)	(Ph)*	2.08 (Me)	9.06	3.02 (Me)
H4	6.37	6.82	6.77	6.54	8.18	8.24
H5	7.05	7.14	7.04	7.21	8.52	8.50
H6	7.09	7.20	7.17	7.27	8.35	8.30
H7	6.74	6.84	6.81	6.93	4.57, 4.57	4.52, 4.52
H8	6.97	7.06	7.01	7.20	7.84	7.74
H9	5.92	6.02	5.99	5.95	6.90	6.85
C3	138.4	143.8	148.3	142.5	151.9	163.8
C3a	127.8	127.4	127.8	127.0	126.4	126.8
C4	111.9	110.4	113.0	110.2	126.8	124.7
C5	128.3	128.1	127.8	127.8	140.3	139.7
C6	123.2	123.5	123.8	123.0	135.6	134.6
C6a	135.9	135.7	136.3	135.6	140.3	140.6
C7	114.5	113.8	114.7	114.3	36.3	36.2
C8	128.4	128.1	128.0	128.2	161.3	159.1
C9	96.6	96.5	96.5	97.0	116.9	116.7
C9a	139.6	139.4	139.5	139.6	151.0	150.1
C9aa	127.7	126.4	128.0	126.8	122.0	121.4
N1	–222.0	–230.3	–228.1	–230.5	–187.8	–188.5
N2	–63.8	–72.3	–66.5	–59.6	–60.5	–69.7

* 3-Phenyl group: H*o* = 7.61, H*m* = 7.40, H*p* = 7.35; C*i* = 138.6, C*o* = 128.4, C*m* = 127.9, C*p* = 128.0.

The experimental ^{1}H 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, R^2 = 0.976. The three NH protons need a correction of 0.80 ppm due to specific solvent effects.

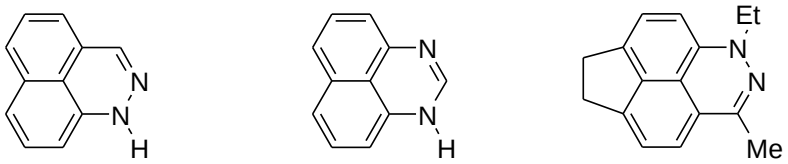
Concerning ^{15}N-shifts, the only experimental data are those of reference[37] – they are consistent with the calculated values for **7a** assuming that the reported data use ammonia as reference compound; we have transformed them to nitromethane reference by subtracting 380.2 ppm (Figure 13).



7a **49** DMSO-d_6 **53** DMSO-d_6

Figure 13. Calculated for **7a** and experimental ^{15}N chemical shifts of **49** and **53** (δ, ppm). For the 7-nitro group of **53** there are two values in reference,[37] one in the main text and the other in the experimental part.

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.



1 **2** **12**

Figure 14. Structures of compounds **1**, **2** and **12**.

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 1*H*-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 1*H*-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 1*H*-benzo[*de*]cinnolines deserve to be explored.

9. Conclusions

The chemistry of 1*H*-benzo[*de*]cinnolines, 6*H*-dibenzo[*de,g*]cinnolines and 1*H*-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

1. Pozharskii, A. F.; Gulevskaya, A. V.; Claramunt, R. M.; Alkorta, I.; Elguero, J. *Russ. Chem. Rev*. **2020**, *89*, 1204–1260. https://doi.org/10.1070/RCR4963
2. Sahiba, N.; Agarwal, S. *Top. Curr. Chem*. **2020**, *378*, 44. https://doi.org/10.1007/s41061-020-00307-5
3. Harry, N. A.; Ujwaldev, S. M.; Aneeja, T.; Anilkumar, G. *Curr. Org. Chem*. **2021**, *25*, 248–271. https://doi.org/ 10.2174/1385272824999201124141506
4. Certain data included herein are derived from Clarivate *Web of Science*. © Copyright Clarivate 2022. All rights reserved.

5. Lacy, P. H.; Smith, D. C. C. *J. Chem. Soc. (C)* **1971**, 747–748.
6. Lacy, P. H.; Smith, D. C. C. *J. Chem. Soc. (Perkin I)* **1975**, 419–420.
7. Aksenova, I. V.; Saprykina, N. G.; Aksenov, A. V. *Russ. J. Org. Chem*. **2008**, *44*, 148–148. https://doi.org/ 10.1134/S1070428008010223
8. Suh, S.-E.; Barros, S. A.; Chenoweth, D. M. *Chem. Sci*. **2015**, *6*, 5128–5132. https://doi.org/ 10.1039/c5sc01726b
9. Su, L.; Hou, W. *Chin. J. Org. Chem*. **2019**, *39*, 363–376. https://doi.org/DOI: 10.6023/cjoc201806021
10. Suh, S.-E.; Chen, S.; Houk, K. N.; Chenoweth, D. M. *Chem. Sci*. **2018**, *9*, 7688–7693. https://doi.org/ 10.1039/c8sc01796d
11. Elguero, J.; Marzin, C.; Katritzky, A. R.; Linda, P. In Advances in Heterocyclic Chemistry: Tautomerism of Heterocycles, Supplement 1. New York: Academic Press, 1976.
12. Catalán, J.; de Paz, J. L. G.; Elguero, J. *J. Chem. Soc., Perkin Trans. 2,* **1996**, 57–60. https://doi.org/ 10.1039/P29960000057
13. Alkorta, I.; Elguero, J. *J. Phys. Org. Chem*. **2005**, *18*, 719–724. https://doi.org/10.1002/poc.923
14. Alkorta, I.; Elguero, J. **2022**; submitted to *Theor. Chem. Acc*.
15. Becke, A. D. *Phys. Rev. A* **1988**, *38*, 3098–3100. https://doi.org/10.1103/PhysRevA.38.3098
16. Frisch, M. J.; Pople, J. A.; Binkley, J. S. *J. Chem. Phys*. **1984**, *80*, 3265–3269. https://doi.org/ 10.1063/1.447079
17. Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Petersson, G. A.; Nakatsuji, H.; Li, X.; Caricato, M.; Marenich, A. V.; Bloino, J.; Janesko, B. G.; Gomperts, R.; Mennucci, B.; Hratchian, H. P.; Ortiz, J. V.; Izmaylov, A. F.; Sonnenberg, J. L.; Williams-Young, D.; Ding, F.; Lipparini, F.; Egidi, F.; Goings, J.; Peng, B.; Petrone, A.; Henderson, T.; Ranasinghe, D.; Zakrzewski, V. G.; Gao, J.; Rega, N.; Zheng, G.; Liang, W.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Throssell, K.; Montgomery, Jr., J. A.; Peralta, J. E.; Ogliaro, F.; Bearpark, M. J.; Heyd, J. J.; Brothers, E. N.; Kudin, K. N.; Staroverov, V. N.; Keith, T. A.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A. P.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Millam, J. M.; Klene, M.; Adamo, C.; Cammi, R.; Ochterski, J. W.; Martin, R. L.; Morokuma, K.; Farkas, O.; Foresman, J. B; Fox, D. J. (2016) Gaussian 16, Revision A.03, Gaussian, Inc., Wallingford CT.
18. Cancès, E.; Mennucci, B.; Tomasi, J. *J. Chem. Phys*. **1997**, *107*, 3032–3041. https://doi.org/10.1063/ 1.474659
19. Groom, C. R.; Bruno, I. J.; Lightfoot, M. P.; Ward, S. C. *Acta Crystallogr*. *Sect. B* **2016**, *72*, 171–179. https://doi.org/ 10.1107/S2052520616003954
20. Langhals, H.; Ismael, R.; Polborn, K. *Z. Kristallogr.-New Cryst. Struct*. **1999**, *214*, 35–37.
21. Elisevich, D. M.; Mezheritskii, V. V.; Dorofeenko, G. N. *Zh. Org. Khim*., *English Translation*, **1981**, *17*, 1566–1570.
22. Omelichkin, N. I.; Minyaeva, L. G.; Mezheritskii, V. V. *Russ. J. Org. Chem*. **2017**, *53*, 258–262. https://doi.org/ 10.1134/S1070428017020208
23. Gineityte, V. *J. Mol. Struct. Theochem* **2006**, *760*, 229–234.
24. Schofield, K. *Aromatic Nitrations*, Cambridge University Press, Cambridge, 1980.
25. Hernando, E.; Castillo, R. R.; Rodríguez, N.; Gómez Arrayás, R.; Carretero, J. C. *Chem. Eur. J*. **2014**, *20*, 13854–13859.

https://doi.org/10.1002/chem.201404000
26. Dou, Y.; Yin, B.; Zhang, P.; Zhu, Q. *Eur. J. Org. Chem*. **2018**, 4571–4576. https://doi.org/10.1002/ ejoc.201800912
27. Moodie, R. B.; Schofield, K.; Williamson, M. J. *Chem. Ind*. **1963**, 1283–1284.
28. Mezheritskii, V. V.; Minyaeva, L. G.; Omelichkin, N. I.; Borodkin, G. S.; Korobov, M. S. *Russ. J. Org. Chem*. **2015**, *51*, 670–673. https://doi.org/10.1134/S1070428015050152
29. Omelichkin, N. I.; Minyaeva, L. G.; Mezheritskii, V. V. *Russ. J. Org. Chem*. **2017**, *53*, 1075–1080. https://doi.org/ 10.1134/S1070428017070193
30. Omelichkin, N. I.; Minyaeva, L. G.; Milov, A. A.; Kuz'mina, L. G.; Mezheritskii, V. V. *Russ. J. Org. Chem*. **2018**, *54*, 1205–1212. https://doi.org/10.1134/S1070428018080146
31. Groom, C. R.; Bruno, I. J.; Lightfoot, M. P.; Ward, S. C. *Acta Crystallogr. Sect. B* **2016**, *72*, 171–179. https://doi.org/10.1107/S2052520616003954
32. Omelichkin, N. I.; Minyaeva, L. G.; Mezheritskii, V. V. *Russ. J. Org. Chem*. **2016**, *52*, 131–132. https://doi.org/10.1134/S1070428016010255
33. Omelichkin, N. I.; Minyaeva, L. G.; Mezheritskii, V. V. *Russ. J. Org. Chem*. **2016**, *52*, 562–566. https://doi.org/10.1134/S1070428016040151
34. Omelichkin, N. I.; Kuz'mina, L. G.; Minyaeva, L. G.; Mezheritskii, V. V. *Russ. J. Org. Chem*. **2017**, *53*, 477–478. https://doi.org/10.1134/S1070428017030319
35. Omelichkin, N. I.; Kuz'mina, L. G.; Minyaeva, L. G.; Mezheritskii, V. V. *Russ. J. Org. Chem*. **2019**, *55*, 87–92. https://doi.org/10.1134/S107042801901010X
36. Alkorta, I.; Elguero, J. *Struct. Chem*. **2003**, *14*, 377–389. https://doi.org/10.1023/A:1024402027760
37. Claramunt, R. M.; Sanz, D.; López, C.; Jiménez, J. A.; Jimeno, M. L.; Elguero, J.; Fruchier, A. *Magn. Reson. Chem*. **1997**, *35*, 35–75. https://doi.org/10.1002/(SICI)1097-458X(199701)35:1<35::AID-OMR25> 3.0.CO;2-K
38. Pozharskii, A. F.; Malysheva, A. N. *Chem. Heterocycl. Comp*. English Translation, **1970**, *6*, 103–110.
39. Yu, A.; Xue, X.; Wang, J.; Wang, H.; Wang, Y. *J. Phys. Org. Chem*. **2012**, *25*, 92–100. https://doi.org/ 10.1002/poc.1876
40. Tzeli, D.; Kozielewicz, P.; Zloh, M.; Antonow, D.; Tsoungas, P. G.; Petsalakis, I. D. *Chem. Select* **2018**, *3*, 9743–9752. https://doi.org/10.1002/slct.201801627
41. Tzeli, D.; Tsoungas, P. G. *Chem Select* **2021**, *6*, 951–961. https://doi.org/10.1002/slct.202004237
42. Baell, J. B.; Holloway, G. A. *J. Med. Chem*. **2010**, *53*, 2719–2740. https://doi.org/10.1021/jm901137j
43. Szumilak, M.; Stanczak, A. *Molecules* **2019**, *24*, 2271. https://*doi*.org/10.3390/molecules24122271

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