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Heterocycle Synthesis*

Unaromatized Tetrahydrobenzimidazole Synthesis from *p*-Benzoquinone and *N*-Arylamidines and their Cytotoxic Potential

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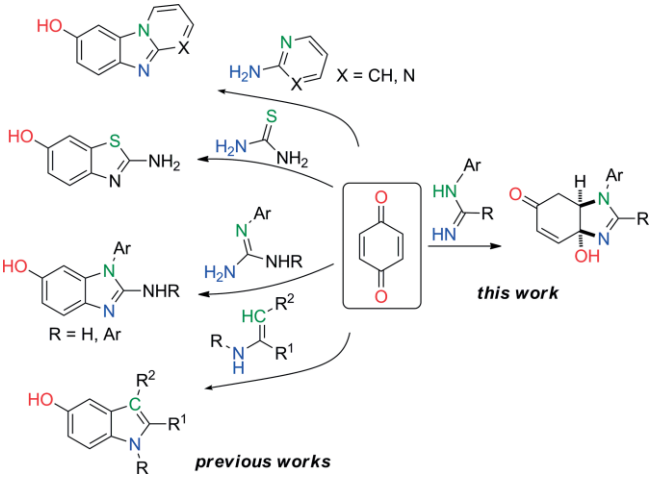
Abstract: A diverse set of unaromatized and densely functionalized tetrahydrobenzimidazole adducts were obtained in good yields by simple mixing *p*-benzoquinone **1** with *N*-arylamidines **2** under mild conditions. The main features of these adducts include a hemi *N,O*-acetal function, and an imidazoline regioselectively and stereoselectively fused with a conjugated cyclohexenone ring. These compounds were evaluated for their cytotoxic potential against hematopoietic cancer cell lines including Jurkat, Raji, K562 and U937 compared to peripheral blood mononuclear cells (PBMCs) from healthy donors. Some of them including **3a**, **3k** and **3l** were found to exhibit significant selective cytotoxicity against cancer cells with IC_{50} values between 3 and 10 μM at 48 hours.

Introduction

Nitrogen containing heterocyclic compounds are extremely important because of their occurrence in various natural products, biologically relevant molecules, as well as synthetic organic compounds with interesting physical properties.[1] The development of new and simple methods of carbon–nitrogen bond formation is obviously of vital importance in organic syntheses and enables the access to a wide range of valuable structures. Although metal catalyzed cross-coupling reactions have emerged as a powerful synthetic tool for such transformations,[2] most of the natural processes for this purpose are based on metal-free reactions which consist in most cases of Schiff base formation, amidation, Mannich and Michael reactions under easy conditions (temperature, pH, solvents…).[3]

Simple access to complex and polyfunctionalized molecules from readily available starting materials is highly desirable in view of the potential applications of the obtained compounds in drug discovery. Belonging to the family of metal-free C–N bond formation, reactions of 1,3-bis-nucleophiles with at least one nitrogen terminus such as enamines,[4] thioureas,[5] 2-aminopyridine,[6] and related 2-amino aza heterocycles[7] with *p*-benzoquinones constitute an efficient method for the construction of different benzazole moieties (indole, benzothiazole, benzimidazole) bearing a hydroxy group in the benzo ring (Scheme 1). Very recently, we reported such a reaction applied for guanidine derivatives as 1,3-bis-nucleophile components as a rapid access to 5- or 6-hydroxy-2-aminobenzimidazoles.[8] Continuing our interest in new efficient methods for carbon–nitrogen bond formation and to design new imidazole derivatives,[9] we have investigated the chemical behavior of amidines to *p*-benzoquinone. We were particularly interested to see, if the interesting result of *N*-arylguanidines leading to 2-amino-6-hydroxybenzimidazoles, could be extended to amidine series to provide 2-carbon substituted 6-hydroxybenzimidazoles.



Scheme 1. *p*-Benzoquinone coupling with 1,3-binucleophyles.

Results and Discussion

As previously remarked,[8] *p*-benzoquinone is highly sensitive to strongly basic reaction conditions and readily polymerized. N-H

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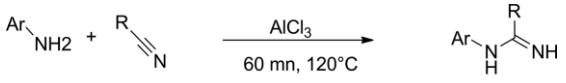
and *N*-alkylated amidines, like their guanidine counterparts, are stronger bases than ordinary alkylamines and accordingly can trigger the polymerization of *p*-benzoquinone, especially in protic media. To tame their basicity while preserving sufficient nucleophilicity, we chose *N*-aryl amidines as model substrates in this study. They were prepared using procedure 1 (Table 1) or procedure 2 (Table 2).[10]

Table 1. Amidine preparation using procedure 1[a].

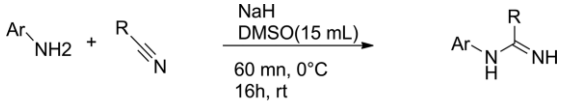


Procedure 1

Entry	Ar	R	Product, Yield [%]
1	C_6H_5	C_6H_5	**2a**, 96
2	3-MeC_6H_4	C_6H_5	**2b**, 92
3	3,5-MeC_6H_4	C_6H_5	**2c**, 94
4	C_6H_5	4-BrC_6H_4	**2h**, 90
5	4-MeC_6H_3	C_6H_5	**2l**, 77
6	C_6H_4	CH_3	**2m**, 81
7	4-ClC_6H_4	CH_3	**2n**, 72
8	4-MeOC_6H_4	CH_3	**2o**, 64
9	C_6H_5	*i*Pr	**2p**, 70
10	C_6H_5	*n*Pr	**2q**, 63

[a] Reaction conditions: aniline/nitrile/$AlCl_3$: 1.02:1:1.02 proportion.

Table 2. Amidine preparation using procedure 2[a].

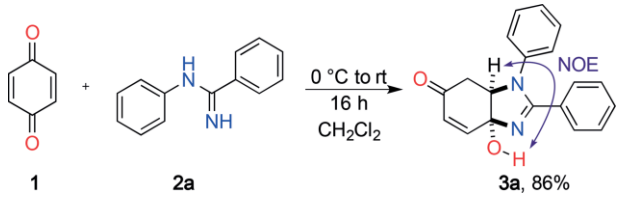


Procedure 2

Entry	Ar	R	Product, Yield [%]
1	2,3-$Me_2C_6H_3$	C_6H_5	**2d**, (85)
2	2,4-$Me_2C_6H_3$	C_6H_5	**2e**, 87
3	2,5-$Me_2C_6H_3$	C_6H_5	**2f**, 91
4	4-MeOC_6H_4	C_6H_5	**2g**, 82
5	C_6H_5	3-MeOC_6H_4	**2i**, 66
6	4-ClC_6H_4	4-BrC_6H_4	**2j**, 92
7	4-ClC_6H_4	C_6H_5	**2k**, 93

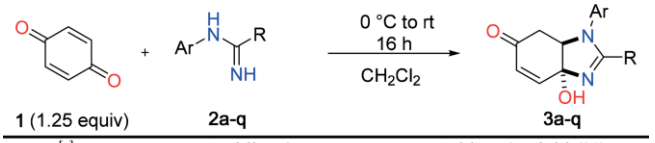
[a] Reaction conditions: 30 mmol of aniline, nitrile and NaOH in DMSO (15 mL).

We started our study by investigating the reaction of *p*-benzoquinone **1** with *N*-phenylbenzamidine **2a** (Scheme 2). Adding **1** into a solution of **2a** in CH_2Cl_2 at room temp. led to the formation of a white precipitate which was characterized by ^1H, ^{13}C NMR, NOESY, and HRMS as **3a** in good yield of 86 % (Table 3). It is important to note that the same reaction carried out in methanol resulted in a resinous mixture of polymerized products issued from *p*-benzoquinone **1**.

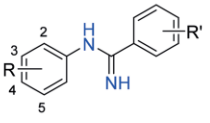
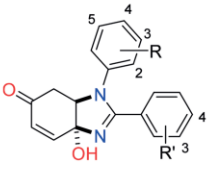
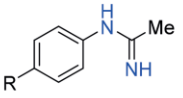
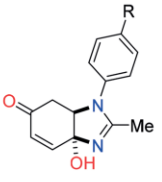
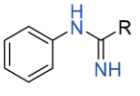
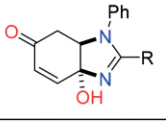


Scheme 2. Reaction of quinone **1** with amidine **2a**.

Table 3. Reaction of *p*-benzoquinone 1 with *N*-arylamidines 2[a] .



1 (1.25 equiv) 2a-q 3a-q

Entry[a]	Amidine **2**	Adduct **3**, yield (%)
		
1	R = R' = H, **2a**	R = R' = H , **3a**, 86
2	R = 3-Me, R' = H, **2b**	R = 3-Me, R' = H, **3b**, 76
3	R = 3,5-Me_2, R' = H, **2c**	R = 3,5-Me_2, R' = H, **3c**, 72
4	R = 2,3-Me_2, R' = H, **2d**	R = 2,3-Me_2, R' = H, **3d**[b], 70
5	R = 2,4-Me_2, R' = H, **2e**	R = 2,4-Me_2, R' = H, **3e**[b], 75
6	R = 2,5-Me_2, R' = H, **2f**	R = 2,5-Me_2, R' = H, **3f**[b], 73
7	R = 4-OMe, R' = H, **2g**	R = 4-OMe, R' = H, **3g**, 80
8	R = H, R' = 4-Br, **2h**	R = H, R' = 4-Br, **3h**, 81
9	R = H, R' = 3-OMe, **2i**	R = H, R' = 3-OMe, **3i**, 81
10	R = 4-Cl, R' = 4-Br, **2j**	R = 4-Cl, R' = 4-Br, **3j**, 74
11	R = 4-Cl, R' = H, **2k**	R = 4-Cl, R' = H , **3k**, 77
12	R = 4-Me, R' = H, **2l**	R = 4-Me, R' = H , **3l**, 80
		
13	R = H, **2m**	R = H, **3m**, 73
14	R = Cl, **2n**	R = Cl, **3n**, 74
15	R = OMe, **2o**	R = OMe, **3o**, 78
		
16	R = *i*-Pr, **2p**	R = *i*-Pr, **3p**, 84
17	R = *n*-Pr, **2q**	R = *n*-Pr, **3q**, 79

[a] Reaction conditions: **1** (2.5 mmol), **2** (2 mmol) in CH_2Cl_2 (12 mL). [b] Mixture of atropisomers.

The scope of this process was examined by testing several *N*-aryl benzamidines with *p*-benzoquinone (Table 3). A wide

range of substitution patterns, such as Me, OMe, Cl, Br can be used. In all cases, the target adducts were easily obtained in high yields by precipitation or simple filtration by flash chromatography.

This protocol was also extended to aliphatic amidines **2m**–**q** to provide the corresponding adducts. Without modification, the standard conditions resulted in adducts **3m**–**q** in good yields (Table 3, entries 13–17). However, our method is limited to the unsubstituted *p*-benzoquinone. With other alkyl-*p*-benzoquinones (Me, Bn, Ph), decomposition of alkylquinones was observed while amidine **2a**, remained unchanged.

The structure of **3d**, a dimethyl derivative of **3a** was confirmed by X-ray crystallography[11] (Figure 1) and shows the main features of this family of poly-functionalized adducts, including a hemi *N*,*O*-acetal function and an imidazoline regioselectively and stereoselectively fused with a conjugated cyclohexenone ring. Although the crystal structure of **3d** revealed one atropisomer, the ^{1}H NMR spectrum showed the presence of atropisomers mixture. In fact, all compounds having a methyl group at position 2 of the N-Ar group were obtained as a mixture of atropisomers.

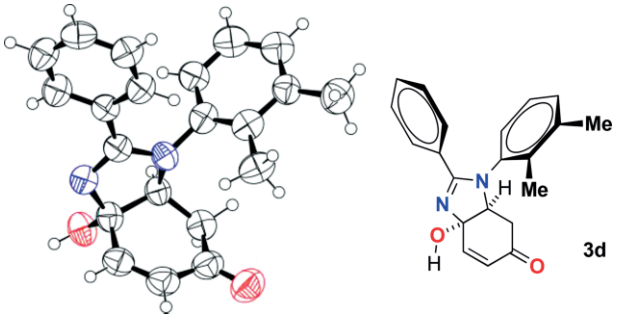
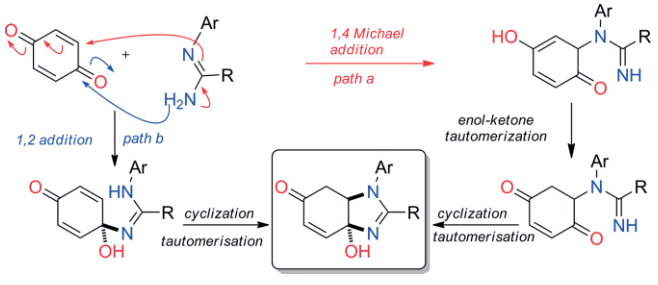


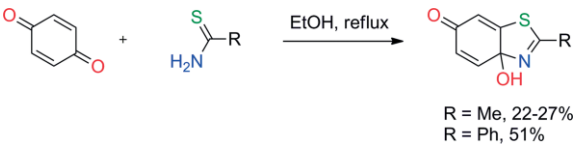
Figure 1. X-ray analysis of **3d**. Displacement ellipsoids are shown at the 50% probability level.

Regarding the regioselectivity of the present reaction, the mechanism could consist of a Michael addition (*path a*) involving the nitrogen bearing the aromatic substituent, followed by an enol-ketone tautomerization and a nucleophilic attack by the unsubstituted nitrogen atom (Scheme 3). The alternative would be a 1,2 addition attack by the unsubstituted nitrogen first followed by the intramolecular Michael addition tolerating the sterically hindered nitrogen (*path b*).



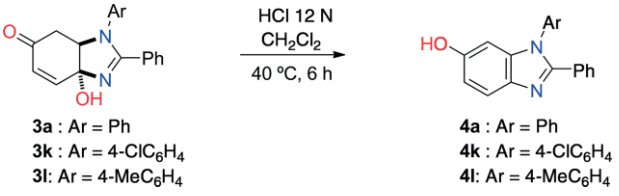
Scheme 3. Proposed reaction pathway.

Regarding the absence of aromatizing dehydration step, we are currently investigating the reaction and the resulting compounds for the understanding of the amazing relative stability of the aminocarbinol derivative. We found only one related example of addition of thioacetamide and thiobenzamide to *p*-benzoquinone resulting in non-dehydrated adducts but already oxidized by *p*-benzoquinone (Scheme 4).[12]



Scheme 4. Non-dehydrated oxidized adduct of quinone **1** with thioamides.[11]

Dehydration-aromatization of **3a**, **3k and 3l** in acidic condition by treating with 12 N HCl in CH_2Cl_2 at 40 °C for 6 h led to **4a** (85 %), **4k** (75 %) and **4l** (79 %) (Scheme 5). Other reactions using the tetrahydrobenzimidazoles of type **3** are currently under investigation.



Scheme 5. Dehydrated/aromatization of **3** into **4** in acidic conditions.

Among these synthetized compounds, **3a**, **3k** and **3l** exhibited significant cytotoxicity against U937, K562, Jurkat and Raji cells with IC_{50} values between 3 and 9.5 μM after 48 hours of exposure (Table 4). At the IC_{50} values, these compounds are non-toxic against healthy cells (PBMCs) demonstrating increased antiproliferative properties which suggest a potential selective toxicity in vivo (Figure 2). In opposition, dehydration products **4a**, **4k** and **4l** were very weakly toxic in K562 cells

Table 4. IC_{50} values of cytotoxic compounds after 48 h of exposure.

	IC_{50} [μM]			
	K562	U937	Raji	Jurkat
3a	7.1 ± 1.3	5.6 ± 0.8	9.5 ± 0.8	7.5 ± 0.4
3k	5.9 ± 0.6	3.2 ± 0.5	5.9 ± 0.2	5.4 ± 0.3
3l	5.8 ± 0.2	3.2 ± 0.6	7.0 ± 1.0	5.0 ± 0.6
Shikonin	1.0 ± 0.1	nd	nd	nd
Etoposide	> 200	nd	nd	nd

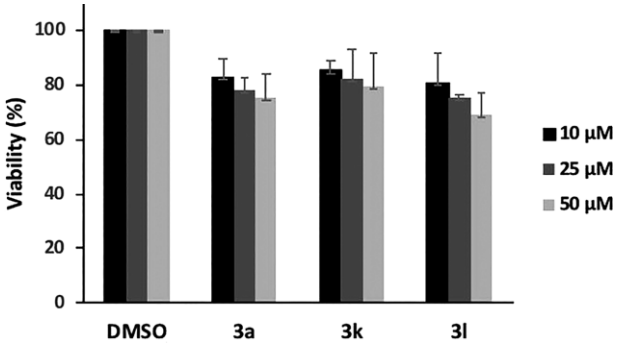


Figure 2. Effect of **3a**, **3k**, and **3l** on healthy cells (PBMCs) at 48 h. Each result is average ± sd of three independents tests.

with IC50s > 50 μM after 48 hours of treatment. Components 2a, 2k and 2l did not present any toxicity under the same conditions. Shikonin, a cytotoxic naphthoquinone, and topoisomerase II inhibitor etoposide (VP-16; Etopophos) were used as positive controls in K562 cells (Table 4).

Conclusions

In conclusion, a ready access to densely functionalized adducts of *p*-benzoquinone **1** and *N*-arylamidines **2** has been developed. The new method requires only inexpensive reagents, simple reaction conditions at room temperatures and tolerates a wide range of useful functional groups. All these characters make these adducts **3** attractive not only as a new scaffold of great medicinal interest[13] but also as a template for the synthesis of natural products. Studies aimed at exploiting the versatility of this structure are underway.

Among these new compounds, the cytotoxic ones including **3a**, **3k** and **3l** are potential anticancer molecules to be investigated in our further studies.

Experimental Section

Unless otherwise noted, reagents and solvents were purchased from commercial supplier and used without further purification. Analytical thin layer chromatography (TLC) was purchased from Macherey–Nagel Alugram F/UV 254. Visualization of the chromatogram was performed by UV light (254 nm) and vanilline stains. Flash column chromatography was carried out using Kieselgel 60 μm particle sized silica gel (230-400 mesh). NMR spectra were recorded on Spectrometers Avance 300 MHz and 500 MHz Bruker. Chemical shifts are reported in (δ)ppm relative to tetramethylsilane (TMS) with the residual solvent as internal reference ($CDCl_3$, δ = 7.24 ppm for ^1H and δ = 77.2 ppm for ^{13}C; [D_6]DMSO, δ = 2.50 ppm for ^1H and δ = 39.5 ppm for ^{13}C. CD_3OD, δ = 3.31 ppm for ^1H and δ = 49.1 ppm for ^{13}C). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constants [Hz] and integration. HRMS mass spectra were obtained using electrospray source (Lockspray) coupled with a time flight analyser (LCT, Micromass). Samples were prepared in methanol and injected in the MS system using a Waters 2795 system.

Preparation of *N*-Arylamidines (2).[10a]

Procedure 1: To aniline (6.14 g, 67.0 mmol) was added benzonitrile (6.85 g, 66.0 mmol) and, during about 20 minutes, $AlCl_3$ (8.90 g, 67.0 mmol) with thorough stirring. The mixture is then heated at 120 °C for 60 minutes. Ice-water (300 mL) was then added to the hot mixture while maintaining vigorous stirring. Concentrated aqueous NaOH was added until a pH of 14 was reached and the aqueous layer was extracted with $CHCl_3$ (3 × 30 mL). The combined organic layers were dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was either purified by silica gel chromatography or recrystallization. The yields are given in Table 1 and ^1H NMR spectroscopic data in the supporting information.

Procedure 2: A round-bottomed flask (250 mL in volume) equipped with a stir bar was charged with NaH 50 % (1.58 g, 30.0 mmol) under Ar condition. DMSO (15 mL) was added, and the resulting suspension was cooled with an ice-water bath prior to the addition of the aniline (3.84 g, 30.0 mmol) and the carbonitrile (30.0 mmol). The mixture was kept at 0 °C for 60 min and then stirred for 16 h at room temperature. Ice-water (150 mL) was added while maintaining vigorous stirring. The resulting precipitate was filtered, then triturated and washed with heptane. The residue was then dried under vacuum. The yields are given in Table 2 and ^1H NMR spectroscopic data in the supporting information.

Procedure for the Preparation of Tetrahydrobenzimidazoles 3: To a solution of **2** (2 mmol) in CH_2Cl_2 (6 mL) at 0 °C was added dropwise a solution of **1** (2.5 mmol) in CH_2Cl_2 (6 mL). The resulting mixture was stirred at room temp. for 16 h. The product was washed with heptane or other appropriate solvent (4-8 mL) or purified by flash column chromatography. The yields are given in Table 3.

Characterization of Products 3

(3a*R*,7a*R*)-3a-Hydroxy-1,2-diphenyl-7,7a-dihydro-1*H*-benzo[*d*]-imidazol-6(3aH)-one (3a): Purification by washing with heptane afforded the yellow solid product **3a**. White solid (261 mg, 86 %), m.p. 121 °C. ^1H NMR (500 MHz, [D_6]DMSO): δ = 7.34–7.20 (m, 8 H), 6.94 (d, *J* = 7.4 Hz, 2 H), 6.79 (s, 1 H), 6.67 (d, *J* = 7.1 Hz, 1 H), 5.95 (d, *J* = 7.1 Hz, 1 H), 4.11 (m, 1 H), 2.85 (dd, *J* = 16.8, 2.8 Hz, 1 H), 2.46 (dd, *J* = 16.8 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, [D_6]DMSO): δ = 196.6, 162.6, 144.8, 140.8, 130.3, 130.1, 129.5, 128.5, 128.0, 127.0, 126.7, 125.5, 90.9, 69.7, 36.4 ppm. IR (neat): $\tilde{\nu}_{max}$ = 3021, 2972, 1735, 1685, 1591, 1560, 1490, 1446, 1373, 1271, 1130, 1036 cm^{-1}. HRMS (ESI$^+$) *m/z* $[M + H]^+$ calcd. for $C_{19}H_{17}N_2O_2$ 305.1290, found 305.1275.

(3a*R*,7a*R*)-3a-Hydroxy-2-phenyl-1-(m-tolyl)-7,7a-dihydro-1*H*-benzo[*d*]imidazol-6(3aH)-one (3b): Purification by washing with heptane afforded the pale yellow solid product **3b**. Pale yellow solid (243 mg, 76 %), m.p. 119 °C. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.36–7.27 (m, 3 H), 7.22–7.11 (m, 3 H), 7.01 (d, *J* = 7.7 Hz, 1 H), 6.90 (dd, *J* = 10.4, 1.7 Hz, 1 H), 6.76–6.71 (m, 2 H), 5.99 (d, *J* = 10.4 Hz, 1 H), 4.25 (m, 1 H), 2.81 (dd, *J* = 6.9, 4.7 Hz, 1 H), 2.68 (dd, *J* = 6.9, 3.4 Hz, 1 H), 2.24 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 197.2, 165.1, 144.6, 140.0, 139.8, 136.8, 130.9, 129.6, 129.1, 128.8, 128.4, 128.2, 126.3, 124.8, 116.4, 90.9, 70.1, 36.8, 21.5 ppm. IR (neat): $\tilde{\nu}_{max}$ = 3023, 2969, 1737, 1678, 1555, 1485, 1446, 1373, 1286, 1216, 1123, 1043 cm^{-1}. HRMS (ESI$^+$) *m/z* $[M + H]^+$ calcd. for $C_{20}H_{19}N_2O_2$ 319.1447, found 319.1445.

(3a*R*,7a*R*)-1-(3,5-Dimethylphenyl)-3a-hydroxy-2-phenyl-7,7a-dihydro-1*H*-benzo[*d*]imidazol-6(3aH)-one (3c): Purification by washing with heptane afforded the pale yellow solid product **3c**. Pale yellow solid (240 mg, 72 %), m.p. 127 °C. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.36 (m, 2 H), 7.28 (m, 1 H), 7.22–7.17 (m, 2 H), 6.90 (d, *J* = 10.1 Hz, 1 H), 6.82 (s, 1 H), 6.54 (s, 2 H), 5.99 (d, *J* = 10.1 Hz, 1 H), 4.24 (m, 1 H), 2.80 (dd, *J* = 16.8, 4.6 Hz, 1 H), 2.68 (dd, *J* = 16.8, 3.3 Hz, 1 H), 2.18 (s, 6 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 197.3, 165.1, 144.7, 139.8, 139.6, 130.8, 129.7, 129.3, 129.1, 128.3, 126.3, 125.3, 116.4, 90.8, 70.0, 36.8, 21.4 ppm. IR (neat): $\tilde{\nu}_{max}$ = 3027, 2969, 1737, 1678, 1588, 1560, 1494, 1448, 1375, 1286, 1210, 1128 cm^{-1}. HRMS (ESI$^+$) *m/z* $[M + H]^+$ calcd. for $C_{21}H_{21}N_2O_2$ 333.1603, found 333.1599.

(3a*R*,7a*R*)-1-(2,3-Dimethylphenyl)-3a-hydroxy-2-phenyl-7,7a-dihydro-1*H*-benzo[*d*]imidazol-6(3aH)-one (3d, Athropisomers Mixture): Purification by washing with heptane afforded the white solid product **3d** (mixture of two atropisomers). White solid (232 mg, 70 %), m.p. 128 °C. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.37–6.95 (m, 8 H), 6.87–6.79 (m, 1 H), 6.02–5.97 (m, 1 H), 4 ppm. 34/4.25 (m, 1 H), 2.75/2.68 (m, 1 H), 2.54–2.46 (m, 1 H), 2.16 (s, 3 H), 1.96–1.83 (s, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 197 ppm. 5/197.1, 165.5/165.3, 145.2/144.7, 139.3/139.2, 138.2/136.9, 136.8/136.1, 131.0/130.9, 129.7/129.6, 129.0/128.9, 128.9/128.6, 128.4, 126.9/126.7, 126.4/126.1, 124.4, 91.1/90.4, 71.2/68.2, 37.0/35.3, 20.7/20.5, 14.7/

14.4. IR (neat): $\tilde{\nu}_{max}$ = 3020, 2972, 1739, 1659, 1540, 1450, 1371, 1291, 1216, 1123, 1021 cm^{-1}. HRMS (ESI^+) *m/z* $[M + H]^+$ calcd. for $C_{21}H_{21}N_2O_2$ 333.1603, found 333.1601.

(3a*R*,7a*R*)-1-(2,4-Dimethylphenyl)-3a-hydroxy-2-phenyl-7,7a-dihydro-1*H*-benzo[*d*]imidazol-6(3aH)-one (3e, Athropisomers Mixture): Purification by washing with heptane afforded the pale yellow solid product **3e** (mixture of atropisomers). Yellow solid (249 mg, 75 %), m.p. 118 °C. ^1H: δ = NMR (500 MHz, $CDCl_3$)δ = 7.40–7.10 (m, 7 H), 6.93 (m, 3 H), 6.00 (m, 1 H), 4.37–4.26 (m, 1 H), 2.78–2.70 (m, 1 H), 2.60–2.47 (m, 1 H), 2.25–2.21 (s, 3 H), 2.04–1.85 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 197.5/197.0, 165.0/164.7, 145.3/144.7, 138.5/137.8, 136.7/135.7, 135.3/134.4, 132.7/132.3, 130.9/130.8, 130.8/130.7, 129.7/129.6, 128.7/128.5, 128.3/128.2, 128.0/126.5, 125.9/125.6, 91.0/90.3, 70.7/67.7, 36.7/35.3, 21.1/21.1, 17.7/17.7. IR (neat): $\tilde{\nu}_{max}$ = 3013, 2969, 1739, 1688, 1553, 1496, 1395, 1293, 1247, 1119, 1029 cm^{-1}. HRMS (ESI^+) *m/z* $[M + H]^+$ calcd. for $C_{21}H_{21}N_2O_2$ 333.1603, found 333.1602.

(3a*R*,7a*R*)-1-(2,5-Dimethylphenyl)-3a-hydroxy-2-phenyl-7,7a-dihydro-1*H*-benzo[*d*]imidazol-6(3aH)-one (3f, Athropisomers Mixture): Purification by washing with heptane afforded the pale yellow solid product **3f** (mixture of two atropisomers). Yellow solid (243 mg, 73 %), m.p. 120 °C. ^1H: δ = NMR (500 MHz, $CDCl_3$)δ = 7.40–7.24 (m, 3 H), 7.21–7.16 (m, 2 H), 7.01–6.78 (m, 1 H), 6.01 (m, 1 H), 4.42–4.27 (m, 1 H), 2.80–2.71 (m, 1 H), 2.60–2.49 (m, 1 H), 2.26–2.25 (s, 3 H), 2.03–1.82 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 197.6/197.1, 165.3/164.8, 145.2/144.6, 137.8/137.4, 137.3/136.9, 136.8, 131.9, 131.6/131.5, 131.0, 129.7, 129.1/128.8, 128.7/128.4, 127.0, 126.2/126.0, 91.1/90.4, 70.7/67.9, 36.9/35.4, 21.0, 17.5/17.4. IR (neat): $\tilde{\nu}_{max}$ = 3068, 2918, 1737, 1674, 1547, 1496, 1375, 1295, 1276, 1193, 1157, 1124, 1038 cm^{-1}. HRMS (ESI^+) *m/z* $[M + H]^+$ calcd. for $C_{21}H_{21}N_2O_2$ 333.1603, found 333.1602.

(3a*R*,7a*R*)-3a-Hydroxy-1-(4-methoxyphenyl)-2-phenyl-7,7a-dihydro-1*H*-benzo[*d*]imidazol-6(3aH)-one (3g): Purification by washing with heptane afforded the pale yellow solid product **3g**. Yellow solid (268 mg, 80 %), m.p. 131 °C. ^1H: δ = NMR (300 MHz, $CDCl_3$)δ = 7.36–7.33 (m, 2 H), 7.29–7.17 (m, 3 H), 6.92–6.86 (m, 3 H), 6.79–6.76 (m, 2 H), 6.00 (d, *J* = 10.4 Hz, 1 H), 4.16 (m, 1 H), 3.74 (s, 3 H), 2.82 (dd, *J* = 7.0 Hz, 4.4 Hz, 1 H), 2.66 (dd, *J* = 7.0, 2.5 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 197.4, 165.4, 158.9, 144.5, 132.7, 130.8, 129.6, 129.3, 129.1, 128.4, 126.3, 116.4, 115.1, 90.8, 70.6, 55.6, 36.7 ppm. IR (neat): $\tilde{\nu}_{max}$ = 3064, 2877, 1741, 1688, 1588, 1550, 1509, 1494, 1445, 1375, 1291, 1274, 1249, 1181, 1157, 1128, 1104, 1036 cm^{-1}. HRMS (ESI^+) *m/z* $[M + H]^+$ calcd. for $C_{20}H_{19}N_2O_3$ 335.1396, found 335.1394.

(3a*R*,7a*R*)-2-(4-Bromophenyl)-3a-hydroxy-1-phenyl-7,7a-dihydro-1*H*-benzo[*d*]imidazol-6(3aH)-one (3h): Purification by washing with heptane afforded the pale yellow solid product **3h**. Yellow solid (311 mg, 81 %), m.p. 132 °C. ^1H NMR (300 MHz, $[D_6]$DMSO): δ = 7.47 (m, 2 H), 7.37–7.20 (m, 5 H), 6.95 (m, 2 H), 6.85 (s, 1 H), 6.67 (d, *J* = 10.2 Hz, 1 H), 5.96 (d, *J* = 10.2 Hz, 1 H), 4.12 (m, 1 H), 2.86 (dd, *J* = 6.8, 4.4 Hz, 1 H), 2.46 (dd, *J* = 6.8, 3.2 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $[D_6]$DMSO): δ = 196.5, 161.7, 144.6, 140.4, 131.1, 130.6, 129.6, 129.5, 126.9, 126.9, 125.6, 123.8, 90.9, 69.7, 36.3 ppm. IR (neat): $\tilde{\nu}_{max}$ = 3054, 2979, 1737, 1685, 1594, 1543, 1487, 1400, 1290, 1274, 1182, 1155, 1124, 1033 cm^{-1}. HRMS (ESI^+) *m/z* $[M + H]^+$ calcd. for $C_{19}H_{16}BrN_2O_2$ 383.0395, found 383.0393.

(3a*R*,7a*R*)-3a-Hydroxy-2-(3-methoxyphenyl)-1-phenyl-7,7a-dihydro-1*H*-benzo[*d*]imidazol-6(3aH)-one (3i): Purification by washing with heptane afforded the pale yellow solid product **3i**. Yellow solid (271 mg, 81 %), m.p. 116 °C. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.31–7.21 (m, 3 H), 7.11–7.05 (m, 1 H), 6.97–6.88 (m, 5 H), 6.84–6.80 (m, 1 H), 6.02 (d, *J* = 10.4 Hz, 1 H), 4.24 (m, 1 H), 3.58 (s, 3 H), 2.82 (dd, *J* = 16.8, 4.4 Hz, 1 H), 2.67 (dd, *J* = 16.8, 3.3 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 197.2, 165.0, 159.3, 144.6, 140.0, 136.8, 130.5, 129.9, 129.5, 127.9, 127.7, 126.4, 121.6, 117.7, 116.4, 113.8, 90.9, 70.2, 55.4, 36.7 ppm. IR (neat): $\tilde{\nu}_{max}$ = 3054, 2962, 1741, 1683, 1570, 1492, 1395, 1288, 1254, 1182, 1145, 1116, 1044 cm^{-1}. HRMS (ESI^+) *m/z* $[M + H]^+$ calcd. for $C_{20}H_{19}N_2O_3$ 335.1396, found 335.1389.

(3a*R*,7a*R*)-2-(4-Bromophenyl)-1-(4-chlorophenyl)-3a-hydroxy-7,7a-dihydro-1*H*-benzo[*d*]imidazol-6(3aH)-one (3j): Purification by washing with heptane afforded the pale yellow solid product **3j**. Pale yellow solid (309 mg, 74 %), m.p. 123 °C. ^1H NMR (300 MHz, $[D_6]$DMSO): δ = 7.53–7.49 (m, 2 H), 7.42–7.37 (m, 2 H), 7.26–7.21 (m, 2 H), 6.98–6.92 (m, 2 H), 6.67 (dd, *J* = 10.2, 1.4 Hz, 1 H), 5.95 (d, *J* = 10.2 Hz, 1 H), 4.16 (m, 1 H), 2.88 (dd, *J* = 6.8, 4.4 Hz, 1 H), 2.46 (dd, *J* = 6.8, 3.4 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $[D_6]$DMSO): δ = 196.4, 161.3, 144.6, 139.2, 131.3, 131.2, 130.9, 130.6, 129.6, 129.2, 128.4, 125.7, 123.9, 115.6, 91.0, 69.3, 36.4 ppm. IR (neat): $\tilde{\nu}_{max}$ = 3044, 2944, 1748, 1652, 1622, 1598, 1548, 1487, 1278, 1157, 1128, 1089, 1068, 1009 cm^{-1}. HRMS (ESI^+) *m/z* $[M + H]^+$ calcd. for $C_{19}H_{15}BrClN_2O_2$ 417.0005, found 417.0013.

(3a*R*,7a*R*)-1-(4-Chlorophenyl)-3a-hydroxy-2-phenyl-7,7a-dihydro-1*H*-benzo[*d*]imidazol-6(3aH)-one (3k): Purification by washing with heptane afforded the brown solid product **3k**. Yellow solid (261 mg, 77 %), m.p. 124 °C. ^1H NMR (300 MHz, $[D_6]$DMSO): δ = 7.40–7.28 (m, 7 H), 6.96–6.92 (m, 2 H), 6.85 (s, 1 H), 6.68 (dd, *J* = 10.2, 1.3 Hz, 1 H), 5.95 (d, *J* = 10.2 Hz, 1 H), 4.15 (m, 1 H), 2.88 (dd, *J* = 16.8, 4.3 Hz, 1 H), 2.47 (d, *J* = 16.8 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $[D_6]$DMSO): δ = 196.5, 162.3, 144.8, 139.6, 130.8, 130.3, 130.0, 129.5, 128.6, 128.4, 128.2, 128.0, 125.6, 115.6, 91.0, 69.3, 36.4 ppm. HRMS (ESI^+) *m/z* $[M + H]^+$ calcd. for $C_{19}H_{16}ClN_2O_2$ 339.0900, found 339.0878.

(3a*R*,7a*R*)-3a-Hydroxy-2-phenyl-1-(*p*-tolyl)-7,7a-dihydro-1*H*-benzo[*d*]imidazol-6(3aH)-one (3l): Purification by washing with heptane afforded the white solid product **3l**. White solid (256 mg, 80 %), m.p. 121 °C. ^1H NMR (300 MHz, $[D_6]$DMSO): δ = 7.35–7.21 (m, 5 H), 7.13 (d, *J* = 8.2 Hz, 2 H), 6.84–6.79 (m, 3 H), 6.65 (d, *J* = 10.2 Hz, 1 H), 5.94 (d, *J* = 10.2 Hz, 1 H), 4.02 (m, 1 H), 2.83 (dd, *J* = 16.7, 4.3 Hz, 1 H), 2.44 (dd, *J* = 16.7, 2.9 Hz, 1 H), 2.24 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $[D_6]$DMSO): δ = 196.7, 162.9, 144.7, 138.3, 136.2, 130.4, 130.1, 128.5, 128.0, 127.0, 125.4, 90.8, 70.0, 36.3, 20.5 ppm. IR (neat): $\tilde{\nu}_{max}$ = 3024, 2981, 1741, 1688, 1590, 1559, 1511, 1494, 1445, 1370, 1356, 1271, 1181, 1152, 1124, 1050, 1027 cm^{-1}. HRMS (ESI^+) *m/z* $[M + H]^+$ calcd. for $C_{20}H_{19}N_2O_2$ 319.1447, found 319.1445.

(3a*R*,7a*R*)-3a-hydroxy-2-methyl-1-phenyl-7,7a-dihydro-1*H*-benzo[*d*]imidazol-6(3aH)-one (3m): Purification by washing with heptane afforded the grey solid product **3m**. Brown solid (180 mg, 73 %), m.p. 103 °C. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.43–7.27 (m, 4 H), 7.08–7.04 (m, 2 H), 6.76 (dd, *J* = 10.3, 1.4 Hz, 1 H), 5.98 (d, *J* = 10.3 Hz, 1 H), 4.31 (m, 1 H), 2.75 (dd, *J* = 16.8, 4.6 Hz, 1 H), 2.51 (dd, *J* = 16.8, 2.7 Hz, 1 H), 1.83 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 196.8, 164.2, 144.7, 137.9, 130.1, 128.1, 127.0, 126.0, 90.3, 68.2, 53.6, 36.1, 15.5 ppm. HRMS (ESI^+) *m/z* $[M + H]^+$ calcd. for $C_{14}H_{15}N_2O_2$ 243.1134, found 243.1131. IR (neat): $\tilde{\nu}_{max}$ = 3051, 2989, 1736, 1690, 1579, 1492, 1405, 1295, 1184, 1148, 1121, 1077, 1036 cm^{-1}.

(3a*R*,7a*R*)-1-(4-Chlorophenyl)-3a-hydroxy-2-methyl-7,7a-dihydro-1*H*-benzo[*d*]imidazol-6(3aH)-one (3n): Purification by washing with heptane afforded the grey solid product **3n**. Grey solid (205 mg, 74 %), m.p. 116 °C. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.40–7.37 (m, 2 H), 7.00 (m, 2 H), 6.75 (dd, *J* = 10.2, 1.4 Hz, 1 H), 5.98 (d, *J* = 10.2 Hz, 1 H), 4.27 (m, 1 H), 2.76 (dd, *J* = 17.0, 4.5 Hz, 1 H), 2.48 (dd, *J* = 17.0, 2.4 Hz, 1 H), 1.83 (s, 3 H) ppm. ^{13}C NMR

(75 MHz, $CDCl_3$): δ = 196.5, 163.9, 144.5, 136.5, 134.0, 130.4, 128.2, 126.1, 116.5, 90.4, 68.2, 36.0, 15.5 ppm. IR (neat): $\tilde{\nu}_{max}$ = 3040, 2897, 1734, 1686, 1603, 1586, 1489, 1392, 1283, 1206, 1150, 1116, 1090, 1075 cm^{-1}. HRMS (ESI^+) *m/z* $[M + H]^+$ calcd. for $C_{14}H_{14}ClN_2O_2$ 277.0744, found 277.0743.

(3a*R*,7a*R*)-3a-Hydroxy-1-(4-methoxyphenyl)-2-methyl-7,7a-dihydro-1*H*-benzo[*d*]imidazol-6(3aH)-one (3o): Purification by washing with heptane afforded the grey solid product **3o**. Grey solid (213 mg, 78 %), m.p. 117 °C. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.00–6.97 (m, 2 H), 6.93–6.89 (m, 2 H), 6.74 (dd, *J* = 10.3, 1.4 Hz, 1 H), 5.98 (d, *J* = 10.3 Hz, 1 H), 4.17 (m, 1 H), 2.73 (dd, *J* = 17.0, 4.5 Hz, 1 H), 2.48 (dd, *J* = 17.0, 2.6 Hz, 1 H), 1.78 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 197.2, 164.8, 159.4, 144.7, 130.6, 128.8, 125.9, 116.5, 115.3, 90.3, 68.8, 55.8, 36.2, 15.3 ppm. IR (neat): $\tilde{\nu}_{max}$ = 3030, 2972, 1746, 1686, 1611, 1586, 1509, 1416, 1366, 1291, 1249, 1206, 1148, 1119, 1033 cm^{-1}. HRMS (ESI^+) *m/z* $[M + H]^+$ calcd. for $C_{15}H_{17}N_2O_3$ 273.1239, found 273.1234.

(3a*R*,7a*R*)-3a-Hydroxy-2-isopropyl-1-phenyl-7,7a-dihydro-1*H*-benzo[*d*]imidazol-6(3aH)-one (3p): Purification by washing with heptane afforded the pale yellow solid product **3p**. Yellow solid (228 mg, 84 %), m.p. 121 °C. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.45–7.32 (m, 4 H), 7.11–7.08 (m, 2 H), 6.90 (d, *J* = 10.2 Hz, 1 H), 5.96 (d, *J* = 10.2 Hz, 1 H), 4.18 (m, 1 H), 2.75 (dd, *J* = 7.0, 4.3 Hz, 1 H), 2.48 (dd, *J* = 7.0, 2.5 Hz, 1 H), 2.35 (m, 1 H), 1.11–1.01 (m, 6 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 197.4, 172.7, 144.7, 138.4, 130.3, 128.5, 128.2, 125.5, 116.4, 90.5, 68.8, 36.1, 27.1, 21.2, 20.1 ppm. IR (neat): $\tilde{\nu}_{max}$ = 3044, 2962, 1739, 1685, 1572, 1497, 1412, 1278, 1242, 1143, 1116, 1043 cm^{-1}. HRMS (ESI^+) *m/z* $[M + H]^+$ calcd. for $C_{16}H_{19}N_2O_2$ 271.1447, found 271.1443.

(3a*R*,7a*R*)-3a-Hydroxy-1-phenyl-2-propyl-7,7a-dihydro-1*H*-benzo[*d*]imidazol-6(3aH)-one (3q): Purification by washing with heptane afforded the pale yellow solid product **3q**. Yellow solid (214 mg, 79 %), m.p. 109 °C. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.44–7.30 (m, 3 H), 7.09–7.06 (m, 2 H), 6.86 (d, *J* = 10.2 Hz, 1 H), 5.97 (d, *J* = 10.2 Hz, 1 H), 4.22 (m, 1 H), 2.75 (dd, *J* = 16.9, 4.5 Hz, 1 H), 2.49 (dd, *J* = 16.9, 2.5 Hz, 1 H), 2.06 (m, 2 H), 1.52 (m, 2 H), 0.80 (m, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 197.2, 167.6, 144.8, 138.3, 130.2, 128.4, 128.3, 127.8, 125.6, 116.4, 90.4, 68.6, 36.1, 30.4, 19.7, 13.8 ppm. IR (neat): $\tilde{\nu}_{max}$ = 3034, 2965, 1742, 1681, 1597, 1496, 1451, 1404, 1376, 1290, 1216, 1148, 1119, 1038 cm^{-1}. HRMS (ESI^+) *m/z* $[M + H]^+$ calcd. for $C_{16}H_{19}N_2O_2$ 271.1447, found 271.1444.

Dehydration of 3 Into 4: HCl 12 N (84 μL, 1 mmol, 1 equiv.) was added dropwise to a solution of **3a** (1 mmol) in CH_2Cl_2 (2 mL) at room temp. The resulting solution was stirred at 40 °C for 6 h. After the reaction time, EtOAc/heptane: 5:1 (2-4 mL) and $NaHCO_3$ sat. (1-2 mL) were added to form the precipitate. The precipitate was then filtered and dried under reduced pressure to give **4a**.

Characterization of Products 4

1,2-Diphenyl-1*H*-benzo[*d*]imidazol-6-ol (4a): Brown solid (243 mg, 85 %). ^1H NMR (300 MHz, $[D_6]$DMSO): δ = 9.41 (s, 1 H), 7.59–7.45 (m, 6 H), 7.40–7.32 (m, 5 H), 6.78 (dd, *J* = 8.5, 2.2 Hz, 1 H), 6.52 (d, *J* = 2.2 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $[D_6]$DMSO): δ = 154.6, 150.2, 138.0, 136.8, 136.0, 130.1, 130.0, 129.0, 128.7, 128.7, 128.3, 127.4, 119.8, 112.5, 95.4 ppm.

1-(4-Chlorophenyl)-2-phenyl-1*H*-benzo[*d*]imidazol-6-ol (4k): White solid (242 mg, 75 %). ^1H NMR (300 MHz, $[D_6]$DMSO): δ = 7.62 (d, *J* = 8.8 Hz, 2 H), 7.56 (d, *J* = 8.7 Hz, 1 H), 7.45 (m, 4 H), 7.36 (m, 3 H), 6.79 (dd, *J* = 8.7, 2.3 Hz, 1 H), 6.52 (d, *J* = 2.3 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $[D_6]$DMSO): δ = 155.0, 150.1, 137.8, 135.9, 135.7, 133.0, 130.0, 129.9, 129.3, 129.1, 128.8, 128.4, 119.9, 112.7, 95.3 ppm.

2-Phenyl-1-(*p*-tolyl)-1*H*-benzo[*d*]imidazol-6-ol (4l): Brown solid (237 mg, 79 %). ^1H NMR (300 MHz, CD_3OD): δ = 7.56 (d, *J* = 8.7 Hz, 1 H), 7.49 (m, 2 H), 7.34 (m, 5 H), 7.18 (d, *J* = 8.3 Hz, 2 H), 6.80 (dd, *J* = 8.7, 2.3 Hz, 1 H), 6.50 (d, *J* = 2.3 Hz, 1 H), 2.42 (s, 3 H) ppm. ^{13}C NMR (75 MHz, CD_3OD): δ = 156.3, 153.0, 140.5, 139.4, 137.2, 135.5, 131.7, 131.2, 130.7, 130.5, 129.6, 128.5, 120.4, 114.2, 97.1, 21.3 ppm.

Cytotoxicity Assay: The cytotoxicity tests were performed by the trypan blue exclusion method. The principle of this method is based on the fact that live cells possess intact cell membranes that exclude trypan blue dye whereas dead cells do not. Cells were placed in 24-well plates at 200,000 cells/mL. Different concentrations of tested compounds were added to each well; maximum DMSO concentration was 2 μL/mL in the control. After 48 h, 20 μL of the cell suspension is mixed with 20 μL of trypan blue and the percentage of viability is calculated based on three independent tests.

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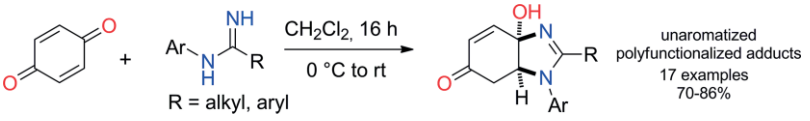
Heterocycle Synthesis*



New tetrahydrobenzimidazoles were synthesized using a simple method from *p*-benzoquinone and *N*-arylamidines, and their cytotoxic potential was evaluated. Among them, three are cytotoxic in the μM range.

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