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## **GRAPHICAL ABSTRACT**



## Synthesis, characterization and X-ray structure of heterocyclic systems prepared via 1,3-dipolar cycloaddition of nitrile oxides with benzimidazolone

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#### Abstract

We report here a one-step synthesis of the new isoxazolyl-benzimidazolones and isoxazolinylbenzimidazolones by 1,3-dipolar cycloaddition of the p-substituted benzonitrile oxides and mesitonitrile oxide with 1-cyclohex-1-en-1-yl-3-propargyl-benzimidazolone or 1-cyclohex-1-en-1-yl-3allyl-benzimidazolone. In all cases these cycloadditions are completely regio- and chemoselective. The structures of new cycloadducts obtained are elucidated by their analytical and spectral data. The relative stereochemistry of the cycloadduct  $\mathbf{8}$  was confirmed by single crystal X-ray analysis.

**Keywords**: Benzimidazolone, 1,3-dipolar cycloaddition, arylonitrile oxides, mesitonitrile oxide, isoxazoles, isoxazolines, chemoselective, regioselective.

#### Introduction

Benzimidazole derivatives started to be envisaged as compounds with biological and medical relevance since the discovery of 5,6-dimethyl-1-( $\alpha$ -D-ribofuranosyl) benzimidazole as part of the structure of vitamin B12 in 1950 [1]. The benzimidazole scaffold is a very useful structural motif in developing molecules of pharmaceutical or biological interest. We find structures benzimidazole-based on several drugs that serve in the diverse areas of medicine and they are applied for his antimicrobial [2-7], antibacterial [8-11], analgesic [12-16], anti-inflammatory [17-18], antioxidant [19-20], anti-cancer [21], antitumor [22], and therapeutically activity [23].

Isoxazoles show pronounced pharmacological applications as anti-inflammatory [24], antimicrobial [25] and anti-cancer agents [26]. Amongst different methods for the preparation of isoxazoles and isoxazolines the 1,3-dipolar cycloaddition is the most important and versatile one. In addition to their potential applications, they can be conveniently modified, allowing thus the transformation of molecules with simple structures into functional complex systems [27-28]. We report here a one-step synthesis of a series of new isoxazoles and isoxazolines heterocycles containing benzimidazolone rings by 1,3-dipolar cycloaddition. This cycloaddition of arylonitrile oxide with benzimidazole derivatives gave a new isoxazolyl-benzimidazolones and isoxazolinyl-benzimidazolones. Our attention has been attracted to synthesizing benzimidazolone ring and its N-alkylation derivatives. Thus, we have used these new dipolarophiles in 1,3-dipolar cycloaddition reaction with some dipoles, that could lead to new benzimidazolone derivatives containing various five-membered heterocycles.

#### **Results and discussion**

Synthesis of the target compounds **5a-d**, **6a-d**, **8** and **9** were successfully achieved as illustrated in schemes 1, 2, 3 and 4. The 1-cyclohex-1-en-1-yl-1*H*-benzimidazol-2(3*H*)-one (**1**) is obtained with a yield 92% by condensation of o-phenylenediamine with ethyl 2-oxocyclohexanecarboxylate in xylene according to the method described by Rossi et al. [29]. The alkylated compounds 1-cyclohex-1-en-1-yl-3-propargyl-1*H*-benzimidazol-2(3*H*)-one (**2**) and 1-allyl-3-cyclohex-1-en-1-yl-1*H*-benzimidazol-2(3*H*)-one (**3**) were obtained on reaction of benzimidazolone **1** with propargyl bromide and allyl bromide, respectively, in the presence of sodium hydroxide and benzyltriethylammonium chloride in benzene (scheme 1), yielding 80-85%. The arylonitrile oxides were prepared in situ during the cycloaddition reaction, from corresponding *p*-substituted benzaldehyde oximes **4a-d** using sodium hypochlorite by a conventional method [30]. The reaction of the dipolarophiles **2** or **3** with the arylonitrile oxides afforded the new isoxazolyl-benzimidazolones **5a-d** (scheme 2) and isoxazolinyl-benzimidazolones **6a-d** (scheme 3). Further, the 2,4,6-trimethylbenzonitrile N-oxide (**7**) was synthesized by treating the mesitaldehyde with hydroxylamine hydrochloride in a basic medium according the chemical literature [31].



The structures of all the compounds were determined analytical and spectroscopic analyses. The known compound (1) was identified by comparison of their spectroscopic data with those reported in the literature [29].

The <sup>1</sup>H NMR spectrum of compound **1** is mainly characterized by the presence of four methylene groups at 1.77-2.44 ppm and a multiplet at 6.02 ppm assigned to the ethylene proton of the cyclohexenyl group. The <sup>13</sup>C NMR reveals in particular five signals at 21.65, 22.60, 24.76, 26.87 and 127.76 ppm assigned to the four methylene groups and to the ethylene carbon (<u>CH=</u>) of the cyclohexenyl and one signal at 154.06 ppm attributed to the carbonyl group.

The <sup>1</sup>H and <sup>13</sup>C NMR spectra of compounds **2** and **3** reveal besides the signals typical of the skeleton of the compound **1** those of the propargyl and the allyl groups respectively.

The 1,3-dipolar cycloaddition reaction between a propargylbenzimidazolone 2 or allylbenzimidazolone 3 with *p*-substituted benzaldehyde oximes 4a-d in the presence of sodium hypochlorite were carried out in chloroform at 0°C afforded new isoxazolylbenzimidazolones 5a-d (scheme 2) and isoxazolinyl-benzimidazolones 6a-d (scheme 3). They were purified by column chromatography and isolated with moderate to quantitative yields (66-85%) (Table 1). No trace of the corresponding stereoisomers has been isolated. This study shows that these reactions are completely chemoselective and regioselective.



Structures of all these new compounds were established on the basis of their analytical and spectral data.

The <sup>1</sup>H NMR spectra of the compounds **5a-d** exhibited a singlet at 6.57, 6.40, 6.40 and 6.51 ppm respectively, due to isoxazolyl protons in position 4<sup>'</sup>. The opposite regioselectivity of the dipolar addition would correspond at 8 ppm to an isoxazolyl proton in position 5<sup>'</sup> [32]. The <sup>13</sup>C NMR spectra of **5a-d** exhibited a signal at 101.26, 101.19, 101.15 and 101.42 ppm respectively, corresponding to C-4<sup>'</sup>, thus confirming the regioselectivity of reaction.

The <sup>1</sup>H NMR spectra of **6a-d** revealed a multiplet at 5.01, 4.96, 5.15 and 5.13 ppm consecutively, due to the isoxazolinyl protons in position 5' and a multiplet at 3.33, 3,29, 3.45 and 3.43 ppm respectively, corresponding to two isoxazolinyl non equivalents protons in position 4'. The regioselectivity of the addition is confirmed by the presence of signals at 79.57, 79.42, 79.81 and 80.59 ppm consecutively of the C-5' isoxazoline ring in the <sup>13</sup>C NMR spectrum [32].

Table 1: Characterization of compounds 1-9

Compound	Melting Yield	Structure of the	Molecular	Mass found [M+H] <sup>+</sup>	
Ĩ	point (°C)	(%)	compounds	formula	Mass calculated $[M+H]^+$

1	181-183	92	N.	$C_{13}H_{14}N_2O$	215.1179
					215.1140
2	118-120	85		C16H16N2O	253.1335
_	110 120		Ň		253.1296
	0.1	00			255.1492
3	Olly	80		$C_{16}H_{18}N_2O$	255.1453
					372.1707
5a	140-142	68		$C_{23}H_{21}N_3O_2$	
					372.1667
					386.1863
5b	156-158	80		$C_{24}H_{23}N_3O_2$	386.1824
				Y	
50	129 140	70			406.1317
50	156-140	38-140 70	NO NO	$C_{23}\Pi_{20}CIN_3O_2$	406.1278
					417 1557
5d	180-182	66		$C_{23}H_{20}N_4O_4$	
			O-N NO		417.1518
					374.1863
6a	158-160	83		$C_{23}H_{23}N_3O_2$	
			C NO		374.1824
7					388.2020
6b	176-178	85		$C_{24}H_{25}N_3O_2$	388.1980
			N <sup>-</sup>		
60	174 176	<u>00</u>			408.1473
6c	1/4-1/6 80	80		$C_{23}\Pi_{22}CIN_3O_2$	408.1434

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64	222-224	76		CarHanNaOa	419.1714
<u>u</u>		70	O <sub>2</sub> N <sup>O</sup>		419.1675
8	112-114	93		$C_{26}H_{27}N_3O_2$	414.2176 414.2137
9	186-188	90		C <sub>26</sub> H <sub>29</sub> N <sub>3</sub> O <sub>2</sub>	416.2333 416.2293

Analogs regioselectivity results have been reported by engaging the dipolarophiles 2 and 3 via 1,3-dipolar cycloaddition reactions with the mesitonitrile oxide 7 prepared outside the reaction medium [31]. This reaction was carried out at room temperature in ether, monocycloadducts 8 and 9 (scheme 4) were obtained with excellent yields (93 and 90%, respectively); this reaction was highly regio- and chemoselective.



The molecular structures of the new heterocyclic systems 1-cyclohex-1-en-1-yl-3-((3-mesitylisoxazol-5-yl)methyl)-1*H*-benzimidazol-2(3*H*)-one (**8**) and 1-cyclohex-1-en-1-yl-3-((3-mesityl-4,5-dihydroisoxazol-5-yl)methyl)-1*H*-benzimidazol-2(3*H*)-one (**9**) were established on the basis of <sup>1</sup>H and <sup>13</sup>C NMR spectroscopic data and High-Resolution Mass Spectrometry (HRMS).

The polyheterocyclic **8** results from the cycloaddition of mesitonitrile oxide **7** to the alkyne group (C=C) of product **2**. In fact, the <sup>1</sup>H NMR spectrum of the compound **8** show a singlet at

6.16 ppm, which corresponds to the proton of the isoxazolyl ring, and two singlets at 2.12, 2.32 ppm assigned to the proton of three methyl groups of the mesityl group. In the <sup>13</sup>C NMR spectrum, the regioselectivity is proved by chemical shift of the isoxazolyl C-4<sup>'</sup> at 104.60 ppm that excluded the opposite dipolar addition [33]. At 20.23 and 21.06 ppm appear the signals of the methyl groups of the mesityl group.

The regioselectivity of the 1,3-dipolar cycloaddition of propargylbenzimidazolone with arylonitrile oxides was confirmed by the X-ray analysis on single crystals of compound **8** (Figure 1); this product crystallizes with ethyl acetate/ethanol (4:1 v/v). This molecule crystallizes in a monoclinic space group *I*2/*a*. A summary of the crystallographic data, selected lengths and binding angles is given in tables 2, 3 and 4, respectively. In the molecular structure of product **8**, the benzimidazole system and the isoxazole fragment are planar. The isoxazole ring wich is normal to the benzimidazole system [dihedral angle is being 65.01(7)°] makes a dihedral angle of 59.31(8)° with his attached mesityl. The carbon–carbon and carbon–nitrogen bond lengths in the isoxazole ring [C(15)-C(16) = 1.348(2) Å, C(16)-C(17) = 1.422(2) Å and C(17)-N(3) = 1.3139(19) Å] agree with their expected double bond character. The endocyclic and exocyclic torsion angles are reported in Table 4. In the crystal, molecules are linked by C(22)---H(22)...O(1) hydrogens bonds.



**Figure 1** : Crystal structure of 1-cyclohex-1-en-1-yl-3-((3-mesitylisoxazol-5-yl) methyl)-1*H*-benzimidazol-2(3*H*)-one (**8**)

Table 2: Crystallographic data and stru	cture refinement for compound 8
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Empirical formula	$C_{26}H_{27}N_3O_2$
Formula weight	413.50
Temperature K	100
Wavelength	1.54184
Crystal system	Monoclinic
Space group	I2/a
Unit cell dimensions	$a = 10.5711 (2) \text{ Å } \alpha = 90$
	b = 23.5384 (3) Å $\beta$ = 104.197 (2)
	$c = 19.2413 (4) \text{\AA} \chi = 90$
Volume ( $Å^3$ )	4641.52 (24)
Z	8
Density (g.cm <sup>-1</sup> )	1.183

Absorption coefficient (mm <sup>-1</sup> )	0.600
F(000)	1760
Theta range for data collection	3.00–74.5°
Index ranges	$-13 \le h \le 13, -29 \le k \le 29, -23 \le l \le 17$
Independent reflections	4721 [R(int) = 0.0799]
Data/restraints/parameters	4721/0/284
Goodness-of-fit on	1.042
R indices (all data)	R1 = 0.0657, wR2 = 0.1334
Largest diff. peak and hole	0.329 and -0.299 eÅ <sup>-3</sup>

# Table 3: Selected bond lengths (Å) for compound ${\bf 8}$

	e v	1	
C1-C2	1.381(2)	C5-H5	0.9500
C1-N2	1.3915(18)	C6-N1	1.3963(19)
C1-C6	1.4035(19)	C7-O1	1.2222(19)
C2-C3	1.400(2)	C7-N2	1.383(2)
C2-H2	0.9500	C7-N1	1.3905(18)
C3-C4	1.393(2)	C8-C9	1.335(2)
C3-H3	0.9500	C8-N1	1.4314(19)
C4-C5	1.400(2)	C8-C13	1.501(2)
C4-H4	0.9500	C9-C10	1.500(2)
C5-C6	1.3835(19)	С9-Н9	0.9500
C10-C11	1.527(2)	C18-C23	1.4079(18)
C10-H10A	0.9900	C18-C19	1.4084(18)
C10-H10B	0.9900	C19-C20	1.394(2)
C11-C12	1.532(2)	C19-C24	1.5113(19)
C11-H11A	0.9900	C20-C21	1.390(2)
C11-H11B	0.9900	С20-Н20	0.9500
C12-C13	1.526(2)	C21-C22	1.400(2)
C12-H12A	0.9900	C21-C25	1.510(2)
C12-H12B	0.9900	C22-C23	1.395(2)
C13-H13A	0.9900	C22-H22	0.9500
C13-H13B	0.9900	C23-C26	1.5161(18)
C14-N2	1.4546(17)	C24-H24A	0.9800
C14-C15	1.4947(19)	C24-H24B	0.9800
C14-H14A	0.9900	C24-H24C	0.9800
C14-H14B	0.9900	C25-H25A	0.9800
C15-C16	1.348(2)	C25-H25B	0.9800
C15-O2	1.3502(19)	C25-H25C	0.9800
C16-C17	1.422(2)	C26-H26A	0.9800
C16-H16	0.9500	C26-H26B	0.9800
C17-N3	1.3139(19)	C26-H26C	0.9800
C17-C18	1.4851(18)	N3-O2	1.4104(17)

## Table 4: Selected angles (°) for compound 8

C2-C1-N2	131.80(13)	C8-C9-C10	122.73(14)
C2-C1-C6	121.67(13)	С8-С9-Н9	118.6
N2-C1-C6	106.53(12)	С10-С9-Н9	118.6
C1-C2-C3	117.10(14)	C9-C10-C11	112.13(12)
С1-С2-Н2	121.5	C9-C10-H10A	109.2

С3-С2-Н2	121.5	C11-C10-H10A	109.2
C4-C3-C2	121.36(14)	C9-C10-H10B	109.2
C4-C3-H3	119.3	C11-C10-H10B	109.2
С2-С3-Н3	119.3	H10A-C10-H10B	107.9
C3-C4-C5	121.26(13)	C10-C11-C12	110.45(14)
С3-С4-Н4	119.4	C10-C11-H11A	109.6
C5-C4-H4	119.4	C12-C11-H11A	109.6
C6-C5-C4	117.23(13)	C10-C11-H11B	109.6
С6-С5-Н5	121.4	C12-C11-H11B	109.6
C4-C5-H5	121.4	H11A-C11-H11B	108.1
C5-C6-N1	131.28(13)	C13-C12-C11	110.31(14)
C5-C6-C1	121.37(13)	C13-C12-H12A	109.6
N1-C6-C1	107.33(12)	C11-C12-H12A	109.6
O1-C7-N2	126.92(13)	C13-C12-H12B	109.6
O1-C7-N1	127.04(14)	C11-C12-H12B	109.6
N2-C7-N1	106.03(12)	H12A-C12-H12B	108.1
C9-C8-N1	119.63(14)	C8-C13-C12	111.28(13)
C9-C8-C13	124.16(14)	C8-C13-H13A	109.4
N1-C8-C13	116.17(12)	C12-C13-H13A	109.4
C8-C13-H13B	109.4	С23-С22-Н22	119.4
C12-C13-H13B	109.4	C21-C22-H22	119.4
H13A-C13-H13B	108.0	C22-C23-C18	119.27(12)
N2-C14-C15	112.98(11)	C22-C23-C26	119.56(12)
N2-C14-H14A	109.0	C18-C23-C26	121.16(12)
C15-C14-H14A	109.0	C19-C24-H24A	109.5
N2-C14-H14B	109.0	C19-C24-H24B	109.5
C15-C14-H14B	109.0	H24A-C24-H24B	109.5
H14A-C14-H14B	107.8	C19-C24-H24C	109.5
C16-C15-O2	110.08(12)	H24A-C24-H24C	109.5
C16-C15-C14	133.52(14)	H24B-C24-H24C	109.5
O2-C15-C14	116.41(12)	С21-С25-Н25А	109.5
C15-C16-C17	104.53(12)	C21-C25-H25B	109.5
C15-C16-H16	127.7	H25A-C25-H25B	109.5
C17-C16-H16	127.7	C21-C25-H25C	109.5
N3-C17-C16	111.34(12)	H25A-C25-H25C	109.5
N3-C17-C18	119.91(12)	H25B-C25-H25C	109.5
C16-C17-C18	128.75(12)	С23-С26-Н26А	109.5
C23-C18-C19	120.22(12)	C23-C26-H26B	109.5
C23-C18-C17	119.02(11)	H26A-C26-H26B	109.5
C19-C18-C17	120.75(12)	C23-C26-H26C	109.5
C20-C19-C18	118.67(12)	H26A-C26-H26C	109.5
C20-C19-C24	118.61(12)	H26B-C26-H26C	109.5
C18-C19-C24	122.72(12)	C7-N1-C6	109.57(12)
$C_{21}$ - $C_{20}$ - $C_{19}$	122.14(13)	C7-N1-C8	123 12(12)
$C_{21} C_{20} C_{1}$	118.9	C6-N1-C8	123.12(12) 127.27(12)
$C_{10}$ $C_{20}$ $U_{20}$	110.7	C7 N2 C1	121.21(12) 110.55(11)
C19-C20-H20	110.9	C/-INZ-CI	110.33(11)

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C20-C21-C22	118.43(13)	C7-N2-C14	122.31(12)		
C20-C21-C25	120.49(14)	C1-N2-C14	127.08(13)		
C22-C21-C25	121.07(14)	C17-N3-O2	105.62(12)		
C23-C22-C21	121.26(13)	C15-O2-N3	108.43(11)		

The <sup>1</sup>H NMR spectrum of the compound **9** is mainly characterized a multiplet at 5.05 ppm, which corresponds to the proton on position 5' of the isoxazolinyl ring and a multiplet at 3.17 ppm attributable to methylene group on position 4'. In the <sup>13</sup>C NMR spectrum, the regioselectivity is proved by chemical shifts of the isoxazolinyl carbons C-4' at 41.98 ppm and C-5' at 78.53 ppm that excluded the opposite dipolar addition.

#### Conclusion

We have synthesized the new classes of isoxazolyl-benzimidazolones and isoxazolinylbenzimidazolones by 1,3-dipolar cycloaddition of the *p*-substituted benzonitrile oxides and mesitonitrile oxide with 1-cyclohex-1-en-1-yl-3-propargyl(allyl)benzimidazolone. In all cases these cycloaddition reactions resulted in a single regioisomer. These reactions are completely chemoselective and regioselective since a single site dipolarophile carbon-carbon of the propargyl (allyl) benzimidazolone group is affected and the sense of addition is unique.

#### **Experimental section**

#### **General methods**

Melting points were taken in an open capillary tube on a Buchi 510 apparatus and are uncorrected. Spectra were recorded with the following instruments: <sup>1</sup>H NMR (300 MHz) and <sup>13</sup>C NMR (75 MHz) spectra were recorded on Bruker spectrometer with chemical shift values given in part per million (ppm) relative to TMS (0.00 ppm). High-Resolution Mass Spectral (HRMS) data were obtained on a Triple TOF<sup>TM</sup> 5600 LC/MS/MS System, (AB SCIEX). The ionization mode used in mass spectra was Ion Spray Voltage (ISVF): 5500. Column chromatography was carried out using E-Merck silica gel 60F<sub>254</sub>. The reaction progress was monitored by Thin Layer Chromatography (TLC) using, silica gel 60-F<sub>254</sub>, and the spots were detected with UV light (254 or 365 nm). IR spectra were recorded on Bruker Vertex 70 spectrometer as potassium bromide discs. The structure of all the compounds was determined by analytical and spectroscopic methods and by comparison with data of the structural related compounds reported in literature. Reagents and solvents were purified in the usual way.

#### I/ Preparation of 1-cyclohex-1-en-1-yl-1*H*-benzimidazol-2(3*H*)-one (1)

A mixture of *o*-phenylenediamine (2.5 g, 23 mmol) and ethyl 2-oxo-cyclohexanecarboxylate (4.4 g, 26 mmol) in xylene (100 mL) was refluxed for 4h. The title compound was isolated by column chromatography using hexane/ethyl acetate (8:2 v/v) as eluent. The 1-cyclohex-1-en-1-yl-1*H*-benzimidazol-2(3*H*)-one (**1**) was obtained as white solid.

Yield: 92%. Mp: 181-183°C (ethanol), (Lit. [29]: 180-181°C). IR (KBr,  $\nu$  (cm<sup>-1</sup>), 3413 (imidazole-NH), 1602 (C=O). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):  $\delta$ ppm: 1.69, 1.78, 2.22, 2.33 (4m, 8H, 4C<u>H<sub>2</sub></u>-cyclohexenyl), 5.90 (m, 1H, =C<u>H</u>-cyclohexenyl), 6.89 - 7.17 (m, 4H, <u>H</u>-Ar), 10.77 (s, 1H, N<u>H</u>). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):  $\delta$ ppm: 21.65, 22.60, 24.76, 26.87 (4<u>C</u>H<sub>2</sub>-

cyclohexenyl), 127.76 (1C, =<u>C</u>H-cyclohexenyl), 108.71, 110.09, 121.38, 121.69 (<u>C</u>H-Ar), 128.44, 130.54, 132.07 (=C-), 154.06 (<u>C</u>=O). HRMS of  $[M+H]^+$  m/z 215.1179, calcd for C<sub>13</sub>H<sub>15</sub>N<sub>2</sub>O, 215.1140.

#### II/ Procedure for alkylation

A mixture of benzimidazolone **1** (1g, 4.7 mmol), benzyltriethylammonium chloride  $(C_6H_5CH_2N(Cl)(C_2H_5)_3)$  (2.3 mmol) and sodium hydroxide aqueous solution (5 mL, 50%) in benzene (25 mL) was stirred at ambient temperature. After 15 min, alkyl (propargyl or allyl) bromide (4.8 mmol) was added slowly. After 6 h of stirring at 25°C, the reaction mixture was diluted with water (30 mL). The organic layer was extracted with dichloromethane (3 × 10 mL), dried over anhydrous sodium sulfate and evaporated under vacuum. The 1-cyclohex-1-en-1-yl-3-propargyl-1*H*-benzimidazol-2(3*H*)-one (**2**) and 1-allyl-3-cyclohex-1-en-1-yl-1*H*-benzimidazol-2(3*H*)-one (**3**) was isolated by column chromatography using hexane/ethyl acetate mixture (9:1 v/v) as eluent.

#### 1-Cyclohex-1-en-1-yl-3-propargyl-1*H*-benzimidazol-2(3*H*)-one (2)

White solid. Yield: 85%. Mp: 118-120°C (ethyl acetate). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):  $\delta$ ppm: 1.63, 1.73, 2.16, 2.40 (4m, 8H, 4C<u>H</u><sub>2</sub>-cyclohexenyl), 2.15 (t, J= 3 Hz, 1H, <u>H</u>C=C), 4.56 (d, J= 3 Hz, 2H, N-C<u>H</u><sub>2</sub>-C), 5.82 (m, 1H, <u>H</u>C=C-cyclohexenyl), 6.89-7.14 (m, 4H, <u>H</u>-Ar). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):  $\delta$ ppm: 21.63, 22.56, 24.71, 26.75 (4<u>C</u>H<sub>2</sub>- cyclohexenyl), 30.37 (1C, N-<u>C</u>H<sub>2</sub>-C), 72.67 (1C, H<u>C</u>=C), 127.41 (1C, =<u>C</u>H-cyclohexenyl), 108.40, 108.74, 121.42, 121.66 (<u>C</u>H-Ar), 128.56, 129.67, 132.15 (=<u>C</u>-), 154.60 (C=O). HRMS of [M+H]<sup>+</sup> m/z 253.1335, calcd for C<sub>16</sub>H<sub>17</sub>N<sub>2</sub>O, 253.1296.

#### 1-Allyl-3-cyclohex-1-en-1-yl-1*H*-benzimidazol-2(3*H*)-one (3)

Oily product. Yield: 80%. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):  $\delta$ ppm: 1.71, 1.79, 2.22, 2.33 (4m, 8H, 4C<u>H</u><sub>2</sub>-cyclohexenyl), 4.38 (d, J = 3Hz, 2H, N-C<u>H</u><sub>2</sub>-C), 5.15 (m, 2H, C<u>H</u><sub>2</sub>=CH), 5.92 (m, 2H, CH<sub>2</sub>=C<u>H</u> and =C<u>H</u>-cyclohexenyl), 6.89-7.14 (m, 4H, <u>H</u>-Ar). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):  $\delta$ ppm: 20.62, 21.54, 23.67, 25.73 (4<u>C</u>H<sub>2</sub>-cyclohexenyl), 42.41 (1C, N-<u>C</u>H<sub>2</sub>-C), 116.59 (C=<u>C</u>H<sub>2</sub>), 126.08 (1C, =<u>C</u>H-cyclohexenyl), 108.40, 108.74, 121.42, 121.66 (-<u>C</u>H=CH<sub>2</sub>, <u>C</u>H-Ar), 128.38, 131.05, 131.06, 131.25 (=<u>C</u>-), 160.81 (C=O). HRMS of [M+H]<sup>+</sup> m/z 255.1492, calcd for C<sub>16</sub>H<sub>19</sub>N<sub>2</sub>O, 255.1453.

#### III/ General procedure for the 1,3-dipolar cycloaddition reactions III-1- Synthesis of cycloadducts 5a-d and 6a-d

To a solution of dipolarophile **2** or **3** (3.97 mmol) and the appropriate *p*-substituted benzaldoximes **4a-d** (9.93 mmol) in chloroform (30 mL), then we added, drop by drop, at 0°C and with vigorous stirring, of bleach at 24° (20 mL). Stirring was continued for 5 hours. The organic layer was dried over anhydrous sodium sulfate (Na<sub>2</sub>SO<sub>4</sub>) and the solvent evaporated under reduced pressure. The residue was then purified by column chromatography eluting with hexane/ethyl acetate mixture (7:3 v/v) to isolate cycloadducts **5a-d** or **6a-d**.

1-Cyclohex-1-en-1-yl-3-((3-phenylisoxazol-5-yl)methyl)-1H-benzimidazol-2(3H)-one (5a)

White solid. Yield: 68%. Mp: 140-142°C (ethanol). IR (KBr, v (cm<sup>-1</sup>): 1706 (C=O), 1612 (C=N). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):  $\delta$ ppm: 1.78, 1.88, 2.32, 2.43 (4m, 8H, 4C<u>H</u><sub>2</sub>-cyclohexenyl), 5.24 (s, 2H, N-C<u>H</u><sub>2</sub>-C), 5.99 (m, 1H, =C<u>H</u>-cyclohexenyl), 6.57 (s, 1H, C<u>H</u>-isoxazolyl), 7.14-7.79 (m, 9H, <u>H</u>-Ar). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):  $\delta$ ppm: 21.59, 22.38, 24.43, 26.75 (4<u>C</u>H<sub>2</sub>-cyclohexenyl), 36.35 (1C, N-<u>C</u>H<sub>2</sub>-C), 101.26 (1C, <u>C</u>H-isoxazolyl), 127.54 (1C, =<u>C</u>H-cyclohexenyl), 108.12, 108.90, 121.42, 121.70, 126.81, 128.87, (<u>C</u>H-Ar), 129.61, 130.10, 132.05 (=<u>C</u>-), 152.59, 162.73, 167.55 (<u>C</u>=N, =<u>C</u>-O, <u>C</u>=O). HRMS of [M+H]<sup>+</sup> m/z 372.1707, calcd for C<sub>23</sub>H<sub>22</sub>N<sub>3</sub>O<sub>2</sub>, 372.1667.

1-Cyclohex-1-en-1-yl-3-((3-p-tolylisoxazol-5-yl)methyl)-1*H*-benzimidazol-2(3*H*)-one (**5**b)

White solid. Yield: 80%. Mp: 156-158°C (ethanol). IR (KBr, v (cm<sup>-1</sup>):1708 (C=O), 1611 (C=N). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):  $\delta$ ppm: 1.63, 1.75, 2.13, 2.28 (4m, 8H, 4C<u>H<sub>2</sub>-cyclohexenyl</u>), 2.28 (s, 3H, C<u>H<sub>3</sub></u>), 5.09 (s, 2H, N-C<u>H<sub>2</sub>-C</u>), 5.85 (m, 1H, =C<u>H</u>-cyclohexenyl), 6.40 (s, 1H, C<u>H</u>-isoxazolyl), 6.98-7.53 (m, 8H, <u>H</u>-Ar). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):  $\delta$ ppm: 21.63, 22.57, 24.73, 26.78 (4<u>C</u>H<sub>2</sub>-cyclohexenyl), 21.42 (1C, <u>C</u>H<sub>3</sub>-Ar), 36.52 (1C, N-<u>C</u>H<sub>2</sub>-C), 101.19 (1C, <u>C</u>H-isoxazolyl), 127.52 (1C,=<u>C</u>H-cyclohexenyl), 108.16, 108.89, 121.70, 121.88, 109.97, 125.79, 126.71, 128.70 (<u>C</u>H-Ar), 129.52, 129.62, 132.07, 140.27, (=<u>C</u>-), 152.61, 162.68, 167.36 (<u>C</u>=N, =<u>C</u>-O, <u>C</u>=O). HRMS of [M+H]<sup>+</sup> m/z 386.1863, calcd for C<sub>24</sub>H<sub>24</sub>N<sub>3</sub>O<sub>2</sub>, 386.1824

1-((3-(4-Chlorophenyl)isoxazol-5-yl)methyl)-3-cyclohex-1-en-1-yl-1*H*-benzimidazol-2(3*H*)-one (**5**c)

White solid. Yield: 70%. Mp: 138-140°C (ethanol). IR (KBr, v (cm<sup>-1</sup>): 1705 (C=O), 1608 (C=N). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):  $\delta$ ppm: 1.63, 1.75, 2.17, 2.28 (4m, 8H, 4C<u>H</u><sub>2</sub>-cyclohexenyl), 5.09 (s, 2H, N-C<u>H</u><sub>2</sub>-C), 6.40 (s, 1H, C<u>H</u>-isoxazolyl), 5.85 (m, 1H, =C<u>H</u>-cyclohexenyl), 6.93-7.58 (m, 8H, <u>H</u>-Ar). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):  $\delta$ ppm: 21.61, 22.56, 24.72, 26.78 (4<u>C</u>H<sub>2</sub>-cyclohexenyl), 36.49 (1C, N-<u>C</u>H<sub>2</sub>-C), 101.15 (1C, <u>C</u>H-isoxazolyl), 127.59 (1C, =<u>C</u>H-cyclohexenyl), 108.06, 108.97, 121.74, 121.97, 127.13, 128.09, 128.62 (<u>C</u>H-Ar), 128.18, 129.63, 132.02, 136.17 (=<u>C</u>-), 152.90, 161.78, 167.92 (<u>C</u>=N, =<u>C</u>-O, <u>C</u>=O). HRMS of [M+H]<sup>+</sup> m/z 406.1317, calcd for C<sub>23</sub>H<sub>21</sub>ClN<sub>3</sub>O<sub>2</sub>, 406.1278.

1-Cyclohex-1-en-1-yl-3-((3-(4-nitrophenyl) isoxazol-5-yl) methyl)-1*H*-benzimidazol-2(3*H*)-one (**5d**)

White solid. Yield: 66%. Mp: 180-182°C (ethanol). IR (KBr, v (cm<sup>-1</sup>): 1705 (C=O), 1608 (C=N). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):  $\delta$ ppm: 1.63, 1.74, 2.11, 2.24 (4m, 8H, 4C<u>H</u><sub>2</sub>-cyclohexenyl), 5.14 (s, 2H, N-C<u>H</u><sub>2</sub>-C), 5.85 (m, 1H, =C<u>H</u>-cyclohexenyl), 6.51 (s, 1H, C<u>H</u>-isoxazolyl), 6.93-8.19 (m, 8H, <u>H</u>-Ar). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):  $\delta$ ppm: 21.60, 22.55, 24.72, 26.78 (4<u>C</u>H<sub>2</sub>-cyclohexenyl), 36.47 (1C, N-<u>C</u>H<sub>2</sub>-C), 101.42 (1C, <u>C</u>H-isoxazolyl), 127.71 (1C, =<u>C</u>H-cyclohexenyl), 107.94, 109.07, 121.79, 122.08, 124.20, 127.67, 128.54 (<u>C</u>H-Ar), 129.65, 131.98, 134.71, 148.75 (=<u>C</u>-), 152.58, 160.95, 168.76 (<u>C</u>=N, =<u>C</u>-O, <u>C</u>=O). HRMS of [M+H]<sup>+</sup> m/z 417.1557, calcd for C<sub>23</sub>H<sub>21</sub>N<sub>4</sub>O<sub>4</sub>, 417.1518.

1-Cyclohex-1-en-1-yl-3-((3-phenyl-4,5-dihydroisoxazol-5-yl)methyl)-1*H*-benzimidazol-2(3*H*)-one **(6a)** 

White solid. Yield: 83%. Mp: 158-160°C (ethanol). IR (KBr, v (cm<sup>-1</sup>): 1699 (C=O), 1612 (C=N). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):  $\delta$ ppm: 1.63, 1.72, 2.18 (3m, 8H, 4C<u>H</u><sub>2</sub>-cyclohexenyl), 3.33 (m, 2H, =C-C<u>H</u><sub>2</sub>-CH-O), 4.03(m, 2H, N-C<u>H</u><sub>2</sub>-CH-O), 5.01 (m, 1H, C<u>H</u>-isoxazolinyl), 5.78 (m, 1H, =C<u>H</u>-cyclohexenyl), 6.83-7.34 (m, 9H, <u>H</u>-Ar). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):  $\delta$ ppm: 21.64, 22.57, 24.69, 26.68 (4<u>C</u>H<sub>2</sub>-cyclohexenyl), 38.07 (1C, =C-<u>C</u>H<sub>2</sub>-CH-O), 44.51 (1C, 1C, N-<u>C</u>H<sub>2</sub>-CH-O), 79.57 (1C, <u>C</u>H-isoxazolinyl), 127.24 (1C, =<u>C</u>H-cyclohexenyl), 108.52, 108.89, 121.49, 121.64, 126.82, 128.65, 129.94, (<u>C</u>H-Ar), 129.27, 129.58, 130.14, 132.24 (=<u>C</u>-), 153.51, 156.80 (<u>C</u>=N, <u>C</u>=O). HRMS of [M+H]<sup>+</sup> m/z 374.1863, calcd for C<sub>23</sub>H<sub>24</sub>N<sub>3</sub>O<sub>2</sub>, 374.1824.

1-Cyclohex-1-en-1-yl-3-((3-p-tolyl-4,5-dihydroisoxazol-5-yl)methyl)-1*H*-benzimidazol-2(3*H*)-one **(6b)** 

White solid. Yield: 85%. Mp: 176-178°C (ethanol). IR (KBr, v (cm<sup>-1</sup>): 1705 (C=O), 1614 (C=N). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):  $\delta$ ppm: 1.66, 1.72, 2.18 (3m, 8H, 4C<u>H</u><sub>2</sub>-cyclohexenyl), 2.24 (s, 3H, C<u>H</u><sub>3</sub>-Ar), 3.29 (m, 2H, =C-C<u>H</u><sub>2</sub>-CH-O), 3.99 (m, 2H, N-C<u>H</u><sub>2</sub>-CH-O), 4.96 (m, 1H, C<u>H</u>-isoxazolinyl), 5.76 (m, 1H, =C<u>H</u>-cyclohexenyl), 6.85-7.38 (m, 8H, <u>H</u>-Ar). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):  $\delta$ ppm: 21.43 (1C, <u>C</u>H<sub>3</sub>-Ar), 21.65, 22.57, 24.70, 26.68 (4<u>C</u>H<sub>2</sub>-cyclohexenyl), 38.16 (1C, =C-<u>C</u>H<sub>2</sub>-CH-O), 44.49 (1C, 1C, N-<u>C</u>H<sub>2</sub>-CH-O), 79.42 (1C, <u>C</u>H-isoxazolinyl), 127.39 (1C, =<u>C</u>H-cyclohexenyl), 108.53, 108.95, 121.48, 121.66, 127.28, 129.37, (<u>C</u>H-Ar), 126.78, 129.52, 129.93, 132.18, 140.42 (=<u>C</u>-), 153.48, 156.80 (<u>C</u>=N, <u>C</u>=O). HRMS of [M+H]<sup>+</sup> m/z 388.2020, calcd for C<sub>24</sub>H<sub>26</sub>N<sub>3</sub>O<sub>2</sub>, 388.1980.

1-((3-(4-Chlorophenyl)-4,5-dihydroisoxazol-5-yl)methyl)-3-cyclohex-1-en-1-yl-1*H*-benzimidazol-2(3*H*)-one (**6c**)

White solid. Yield: 80%. Mp: 174-176°C (ethanol). IR (KBr, v (cm<sup>-1</sup>): 1703 (C=O), 1609 (C=N). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):  $\delta$ ppm: 1.73, 1.82, 2.29 (3m, 8H, 4C<u>H</u><sub>2</sub>-cyclohexenyl), 3.45 (m, 2H, =C-C<u>H</u><sub>2</sub>-CH-O), 4.16 (m, 2H, N-C<u>H</u><sub>2</sub>-CH-O), 5.15 (m, 1H, C<u>H</u>-isoxazolinyl), 5.90 (m, 1H, =C<u>H</u>-cyclohexenyl), 6.99-7.59 (m, 8H, <u>H</u>-Ar). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):  $\delta$ ppm: 21.56, 22.50, 24.65, 26.63 (4<u>C</u>H<sub>2</sub>-cyclohexenyl), 37.84 (1C, =C-<u>C</u>H<sub>2</sub>-CH-O), 44.35 (1C, N-<u>C</u>H<sub>2</sub>-CH-O), 79.81 (1C, <u>C</u>H-isoxazolinyl), 127.63 (1C, =<u>C</u>H-cyclohexenyl), 108.56, 108.81, 121.55, 121.66, 127.43, 128.03 (<u>C</u>H-Ar), 128.92, 129.50, 129.78, 136.17, 132.05 (=<u>C</u>-), 153.50, 155.97 (<u>C</u>=N, <u>C</u>=O). HRMS of [M+H]<sup>+</sup> m/z 408.1473, calcd for C<sub>23</sub>H<sub>23</sub>ClN<sub>3</sub>O<sub>2</sub>, 408.1434.

 $\label{eq:2.1} 1-Cyclohex-1-en-1-yl-3-((3-(4-nitrophenyl)-4,5-dihydroisoxazol-5-yl)methyl)-1H-benzimidazol-2(3H)-one~({\bf 6d})$ 

White solid. Yield: 76%. Mp: 222-224°C (ethanol). IR (KBr, v (cm<sup>-1</sup>): 1706 (C=O), 1612 (C=N). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):  $\delta$ ppm: 1.66, 1.76, 2.21 (3m, 8H, 4C<u>H</u><sub>2</sub>-cyclohexenyl), 3.43 (m, 2H, =C-C<u>H</u><sub>2</sub>-CH-O), 4.11 (m, 2H, N-C<u>H</u><sub>2</sub>-CH-O), 5.13 (m, 1H, C<u>H</u>-isoxazolinyl), 5.80 (m, 1H, =C<u>H</u>-cyclohexenyl), 6.62–8.16 (m, 8H, <u>H</u>-Ar). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):  $\delta$ ppm: 21.64, 22.32, 24.49, 26.62 (4<u>C</u>H<sub>2</sub>-cyclohexenyl), 80.59 (1C, <u>C</u>H isoxazolinyl), 37.39

(1C, =C-<u>C</u>H<sub>2</sub>-CH-O), 44.22 (1C, N-<u>C</u>H<sub>2</sub>-CH-O), 127.71 (1C, =<u>C</u>H-cyclohexenyl), 108.66, 108.70, 121.55, 121.69, 127.52, 123.90 (<u>C</u>H-Ar), 129.50, 129.66, 131.97, 135.17, 148.50 (=<u>C</u>-), 153.53, 155.41 (<u>C</u>=N, <u>C</u>=O). HRMS of  $[M+H]^+$  m/z 419.1714, calcd for C<sub>23</sub>H<sub>23</sub>N<sub>4</sub>O<sub>4</sub>, 419.1675.

#### III-2- Synthesis of cycloadducts 8 and 9

A solution of N-propargylbenzimidazolone 2 (3.97 mmol) or N-allylbenzimidazolone 3 (3.97 mmol) and mesitonitrile oxide 7 [31] (4.7 mmol) in anhydrous diethyl ether (30 mL) was stirred at room temperature to ten days. After evaporating the solvent, the residue obtained is chromatographed by column chromatography eluting with hexane/ethyl acetate mixture (6:4 v/v) to isolate cycloadducts 8 or 9.

1-Cyclohex-1-en-1-yl-3-((3-mesitylisoxazol-5-yl)methyl)-1*H*-benzimidazol-2(3*H*)-one (**8**) White solid. Yield: 93%. Mp: 112-114°C (ethyl acetate). IR (KBr, v (cm<sup>-1</sup>): 1713 (C=O), 1610 (C=N). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δppm: 1.78, 1.88, 2.31, 2.42 (4m, 8H, 4C<u>H</u><sub>2</sub>cyclohexenyl), 2.12, 2.32 (s, 9H, 3C<u>H</u><sub>3</sub>-Ar), 5.27 (s, 2H, N-C<u>H</u><sub>2</sub>-C), 6.00 (m, 1H, =C<u>H</u>cyclohexenyl), 6.16 (s, 1H, C<u>H</u>-isoxazolyl), 6.92-7.29 (m, 6H, <u>H</u>-Ar). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>): δppm: 21.58, 22.53, 24.68, 26.59 (4<u>C</u>H<sub>2</sub>-cyclohexenyl), 20.23, 21.06 (3C, 3<u>C</u>H<sub>3</sub>-Ar), 36.63 (1C, N-<u>C</u>H<sub>2</sub>-C), 104.60 (1C, <u>C</u>H-isoxazolyl), 127.53 (1C, =<u>C</u>H-cyclohexenyl), 108.14, 108.88, 121.61, 121.84, 128.31 (<u>C</u>H-Ar), 125.61, 128.76, 129.65, 132.05, 137.08, 138.84 (=<u>C</u>-), 152.63, 162.38, 166.77 (<u>C</u>=N, =<u>C</u>-O, <u>C</u>=O). HRMS of [M+H]<sup>+</sup> m/z 414.2176, calcd for C<sub>26</sub>H<sub>28</sub>N<sub>3</sub>O<sub>2</sub>, 414.2137. Crystal data for **8**: monoclinic, space group *I*2/*a*, a = 10.5711 (2), b = 23.5384 (3), c = 19.2413 (4)Å, β = 104.197 (2)°, V = 4641.52 (24)Å<sup>3</sup>, Z = 8, 4721 independent reflections, R1 = 0.0657, wR2 = 0.1334.

1-Cyclohex-1-en-1-yl-3-((3-mesityl-4,5-dihydroisoxazol-5-yl)methyl)-1*H*-benzimidazol-2(3*H*)-one **(9)** 

White solid. Yield: 90%. Mp: 186-188°C (ethanol). IR (KBr, v (cm<sup>-1</sup>): 1704 (C=O), 1611 (C=N). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):  $\delta$ ppm: 1.69, 1.76, 2.19, 2.28 (4m, 8H, 4C<u>H<sub>2</sub>-cyclohexenyl</u>), 2.02, 2.15 (s, 9H, 3C<u>H<sub>3</sub>-Aryl</u>), 3.17 (m, 2H, =C-C<u>H<sub>2</sub>-CH-O</u>), 4.08 (m, 2H, N-C<u>H<sub>2</sub>-CH-O</u>), 5.05 (m, 1H, C<u>H</u>-isoxazolinyl), 5.83 (m, 1H, =C<u>H</u>-cyclohexenyl), 6.74-7.24 (m, 6H, <u>H</u>-Ar). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):  $\delta$ ppm: 19.55, 21.07 (3C, 3<u>C</u>H<sub>3</sub>-Ary), 21.66, 22.60, 24.74, 26.78 (4<u>C</u>H<sub>2</sub>-cyclohexenyl), 41.68 (1C, =C-<u>C</u>H<sub>2</sub>-CH-O), 44.58 (1C, N-<u>C</u>H<sub>2</sub>-CH-O), 78.53 (1C, <u>C</u>H-isoxazolinyl), 127.34 (1C, =<u>C</u>H-cyclohexenyl), 108.53, 109,15 121.63, 121.78, 128.44 (<u>C</u>H-Ar), 125.89, 129.55, 129.91, 132.23, 136.45, 138.73 (=<u>C</u>-), 153.68, 157.43 (<u>C</u>=N,<u>C</u>=O). HRMS of [M+H]<sup>+</sup> m/z 416.2333, calcd for C<sub>26</sub>H<sub>30</sub>N<sub>3</sub>O<sub>2</sub>, 416.2293.

#### X-ray crystallography

The analysis and recording of our structure **8** was performed on an Oxford Supernova automatic diffractometer, equipped with a two-dimensional CrysAlis CCD detector, and equipped with an X-ray source using K $\alpha$  radiation of molybdenum. The reflection intensities were collected on a Kappa-CCD diffractometer at 100 K. The structure was solved by direct method and subsequent Fourier analysis. All the hydrogen atoms were located in the Fourier difference map. The programs SHELX-S [34], SHELX-L [35] and WINGX [36] were used

for computations. Crystal data and pertinent details of data collection and refinement are reported in Table 2 for the compound **8**. Table 3 and Table 4 lists selected geometric parameters.

#### Appendix A. Supplementary material

Crystallographic data for **8** have been deposited with the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB22 1eZ, UK (fax: +44 1223 336 033; e-mail: deposit@ccdc.cam.uk or http://www.ccdc.cam.uk) and it is available on request quoting the deposition number CCDC 1820200. Supplementary data associated with this article can be found, in the online version, at http://www.ccdc.cam.ac.uk/Community/blog/2016-12-01.

### References

[1] L.B. Townsend, G.R. Revankar, Benzimidazole nucleosides, nucleotides, and related derivatives, *Chem. Rev.* 70 (1970) 389-438.

[2] P.S. Rathee, R. Dhankar, S. Bhardwaj, M. Gupta, R. Kumar, Synthesis and Antimicrobial studies of novel Benzimidazole derivatives, *J. App. Pharm. Sci.* 01 (2011) 127-130.

[3] A.H. El-masry, H.H. Fahmy, S.H. Ali Abdelwahed, Synthesis and Antimicrobial Activity of Some New Benzimidazole Derivatives, *Molecules* 5 (2000) 1429-1438.

[4] K.F. Ansari, C. Lal, Synthesis, physicochemical properties and antimicrobial activity of some new benzimidazole derivatives, *Eur. J. Med. Chem.* 44 (2009) 4028-4033.

[5] S. Özden, D. Atabey, S. Yıldız, H. Göker, Synthesis and potent antimicrobial activity of some novel methyl or ethyl 1H-benzimidazole-5-carboxylates derivatives carrying amide or amidine groups, *Bioorg. Med. Chem.* 13 (2005) 1587-1597.

[6] M. Tunçbilek, T. Kiper, N. Altanlar, Synthesis and in vitro antimicrobial activity of some novel substituted benzimidazole derivatives having potent activity against MRSA, *Eur. J. Med. Chem.* 44 (2009) 1024-1033.

[7] M. Noolvi, S. Agrawal, H. Patel, A. Badiger, M. Gaba, A. Zambre, Synthesis, antimicrobial and cytotoxic activity of novel azetidine-2-one derivatives of 1H-benzimidazole, *Arabian J. Chem.* 7 (2014) 219-226.

[8] A. Khalafi-Nezhad, M.N. Soltani Rad, H. Mohabatkar, Z. Asraria, B. Hemmateenejad, Design, synthesis, antibacterial and QSAR studies of benzimidazole and imidazole chloroaryloxyalkyl derivatives, *Bioorg. Med. Chem.* 13 (2005) 1931-1938.

[9] C. Hubschwerlen, P. Pflieger, J.L. Specklin, K. Gubernator, H. Gmûnder, P. Angehrn, I. Kompis, Pyrimido[*1,6-a*]benzimidazoles: A New Class of DNA Gyrase Inhibitors, *J. Med. Chem.* 35 (1992) 1385-1392.

[10] P.T.M. Nguyen, J.D. Baldeck, J. Olsson, R.E. Marquis, Antimicrobial actions of benzimidazoles against oral streptococci, *Oral Microbiol. Immunol.* 20 (2005) 93-100.

[11] H. Göker, S. Özden, S. Yıldız, D.W. Boykin, Synthesis and potent antibacterial activity against MRSA of some novel 1,2-disubstituted-1H-benzimidazole-N-alkylated-5-carboxamidines, *Eur. J. Med. Chem.* 40 (2005) 1062-1069.

[12] K.C.S. Achar, K.M. Hosamani, H.R. Seetharamareddy, In-vivo analgesic and antiinflammatory activities of newly synthesized benzimidazole derivatives, *Eur. J. Med. Chem.* 45 (2010) 2048-2054. [13] M. Gaba, D. Singh, S. Singh, V. Sharma, P. Gaba, Synthesis and pharmacological evaluation of novel 5-substituted-1-(phenylsulfonyl)-2-methylbenzimidazole derivatives as anti-inflammatory and analgesic agents, *Eur. J. Med. Chem.* 45 (2010) 2245-2249.

[14] K. Taniguchi, S. Shigenaga, T. Ogahara, T. Fujitsu, M. Matsuo, Synthesis and antiinflammatory and analgesic properties of 2-Amino-1H-benzimidazole and 1,2-Dihydro-2iminocycloheptimidazole Derivatives, *Chem. Pharm. Bull.* 41 (1993) 301-309.

[15] S.M. Sondhi, N. Singh, A. Kumar, O. Lozach, L. Meijer, Synthesis, anti-inflammatory, analgesic and kinase (CDK-1,CDK-5 and GSK-3) inhibition activity evaluation of benzimidazole/benzoxazole derivatives and some Schiff's bases, *Bioorg. Med. Chem.* 14 (2006) 3758-3765.

[16] S.M. Sondhi, N. Singh, M. Johara, A. Kumarb, Synthesis, anti-inflammatory and analgesic activities evaluation of some mono, bi and tricyclic pyrimidine derivatives, *Bioorg. Med. Chem.* 13 (2005) 6158-6166.

[17] S.M. Sondhi, R. Rani, J. Singh, P. Roy, S.K. Agrawal, A.K. Saxena, Solvent free synthesis, anti-inflammatory and anticancer activity evaluation of tricyclic and tetracyclic benzimidazole derivatives, *Bioorg. Med. Chem. Lett.* 20 (2010) 2306-2310.

[18] P.A. Thakurdesai, S.G. Wadodkar, C.T. Chopade, Synthesis and anti-inflammatory activity of some benzimidazole-2-carboxylic acids, *Pharmacologyonline* 1 (2007) 314-329.

[19] A.Ts. Mavrova, D. Yancheva, N. Anastassova, K. Anichina, J. Zvezdanovic, A. Djordjevic, D. Markovic, A. Smelcerovic, Synthesis, electronic properties, antioxidant and antibacterial activity of some new benzimidazoles, *Bioorg. Med. Chem.* 23 (2015) 6317-6326.

[20] C. Kus, G. Ayhan-Kilcigil, S. Özbey, F. BetùlKaynak, M. Kaya, T. Çoban, B. Can-Eke, Synthesis and antioxidant properties of novel N-methyl-1,3,4-thiadiazol-2-amine and 4-methyl-2H-1,2,4-triazole-3(4H)-thione derivatives of benzimidazole class, *Bioorg. Med. Chem.* 16 (2008) 4294-4303.

[21] N.R. Thimmegowda, S.N. Swami, C.S.A. Kumar, Y.C.S. Kumar, S. Chandrappa, W.Y. George, K.S. Rangappa, Synthesis, characterization and evaluation of benzimidazole derivative and its precursors as inhibitors of MDA-MB-231 human breast cancer cell proliferation, *Bioorg. Med. Chem. Lett.* 18 (2008) 432-435.

[22] K. Paul, A. Sharma, V. Luxami, Synthesis and in vitro antitumor evaluation of primary amine substituted quinazoline linked benzimidazole, *Bioorg. Med. Chem. Lett.* 24 (2014) 624-629.

[23] T.D. Penning, G.D. Zhu, V.B. Gandhi, J.C. Gong, S. Thomas, W. Lubisch, R. Grandel, W. Wernet, C.H. Park, E.H. Fry, X.S. Liu, Y. Shi, V. Klinghofer, E.F. Johnson, C.K. Donawho, D.J. Frost, V. Bontcheva-Diaz, J.J. Bouska, A.M. Olson, K.C. Marsh, Y. Luo, S.H. Rosenberg, V.L. Giranda, Discovery and SAR of 2-(1-propylpiperidin-4-yl)-1H-benzimidazole-4-carboxamide: A potent inhibitor of poly(ADP-ribose) polymerase (PARP) for the treatment of cancer, *Bioorg. Med. Chem.* 16 (2008) 6965.

[24] M. Maçzyński, J. Artym, M. Kocięba, I. Kochanowska, S. Ryng, M. Zimecki, Antiinflammatory properties of an isoxazole derivative - MZO-2, *Pharmacol. Rep.* 68 (2016) 894-902.

[25] R. Beniwal, A. Kapoor, Design, synthesis, characterization and antimicrobial evaluation of isoxazole derivatives, *Der Pharmacia Lett.* 8 (2016) 47-54.

[26] A. Kamal, J.S. Reddy, M. Janaki Ramaiah, D. Dastagiri, E. Vijaya Bharathi, M. Ameruddin Azhar, F. Sultana, S.N.C.V.L. Pushpavalli, M. Pal-Bhadra, A. Juvekar, S. Sen, S. Zingde, Design, synthesis and biological evaluation of 3,5-diaryl-isoxazoline/isoxazole-pyrrolobenzodiazepine conjugates as potential anticancer agents, *Eur. J. Med. Chem.* 45 (2010) 3924-3937.

[27] G. Stork, S. Danishefsky, M. Ohashi, The Isoxazole Annelation Reaction. A Method for the Construction of Cyclohexenone Rings in Polycyclic Systems, *J. Am. Chem. Soc.* 89 (1967) 5459-5460.

[28] P.G. Braldi, A. Barco, S. Benetti, S. Manfredini, D. Simoni, Ring Cleavage of 3,5-Disubstituted 2-Isoxazolines by Molybdenum Hexacarbonyl and Water to  $\beta$ -Hydroxy Ketones, *Synthesis* (1987) 276-278.

[29] A. Rossi, A. Hunger, J. Kebrle, K. Hoffmann, Benzimidazol-Derivate und verwandte Heterocyclen VI Die Kondensation von o-Phenylendiamin mit aliphatischen und alicyclischen P-Ketoestern, *Helv. Chim. Acta* 43 (1960) 1298-1313.

[30] G.A. Lee, A Simplified Synthesis of Unsaturated Nirtogen Heterocycles using Nitrile Betaines, *Synthesis* (1982) 508-509.

[31] K.C. Liu, B.R. Shelton, R.K. Howe, A Particularly Convenient Preparation of Benzohydroximinoyl Chlorides (Nitrile Oxide Precursors), *J. Org. Chem.* 45 (1980) 3916-3918.

[32] D. Chiarino, M. Napoletano, A. Sala, 1,3-Dipolar Cycloaddition Synthesis of 3-Bromo-5-Substituted Isoxazoles, Useful Intermediates for the Preparation of Pharmacologically Active Compounds, *J. Heterocyclic Chem.* 24 (1987) 43-46.

[33] H.D. Camara, K. Attar, M. Benchidmi, E.M. Essassi, B. Garriques, Synthesis of new 1hydroxyindole derivatives, *Indian, J. Chem.* 43B (2004) 660-666.

[34] G.M. Sheldrick, Shelxs-97, Program for the solution of crystal structures, University of Göttingen, Germany, 1990.

[35] G.M. Sheldrick, Shelxl-97, Program for crystal structure determination, University of Göttingen, Germany, 1997.

[36] L.J. Farrugia, WINGX-version 1.70.01, single crystal X-ray diffraction data (1997-2005).

### HIGHLIGHTS

- A simple strategy to prepare efficiently isoxazolyl (isoxazolinyl)benzimidazolones
- The nitrile oxides with propargylbenzimidazolone affords isoxazolylbenzimidazolones
- The nitrile oxides with allylbenzimidazolone affords isoxazolinylbenzimidazolones
- These 1,3-dipolar cycloaddition reactions are completely regio- and chemoselective