Taylor & Francis
Taylor & Francis Group

Synthetic Communications

An International Journal for Rapid Communication of Synthetic Organic Chemistry

ISSN: 0039-7911 (Print) 1532-2432 (Online) Journal homepage: http://www.tandfonline.com/loi/lsyc20

Design and synthesis of novel enantiomerically enriched morpholino [4, 3–a] benzimidazole derivatives as potential bioactive agents

Pawankumar R. Tiwari, Marina E. John & Anil V. Karnik

To cite this article: Pawankumar R. Tiwari, Marina E. John & Anil V. Karnik (2018): Design and synthesis of novel enantiomerically enriched morpholino [4, 3–a] benzimidazole derivatives as potential bioactive agents, Synthetic Communications, DOI: 10.1080/00397911.2018.1514052

To link to this article: https://doi.org/10.1080/00397911.2018.1514052

SYNTHETIC COMMUNICATIONS®
https://doi.org/10.1080/00397911.2018.1514052

Taylor & Francis
Taylor & Francis Group

Design and synthesis of novel enantiomerically enriched morpholino [4, 3–a] benzimidazole derivatives as potential bioactive agents

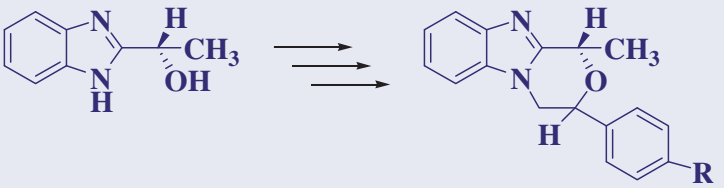
Pawankumar R. Tiwari, Marina E. John, and Anil V. Karnik

Department of Chemistry, University of Mumbai, Mumbai, India

ABSTRACT

A series of chiral morpholino [4, 3-a] benzimidazole derivatives were synthesized effectively from (*S*)-(-)-2-(α-hydroxyethyl)-benzimidazole and phenacyl bromide derivatives using an efficient synthetic protocol in good yields and moderate diastereoselectivities. The substrate controlled diastereoselective route makes available structurally attractive morpholine-fused benzimidazole derivatives with two chiral centers in enantiomerically enriched forms. The preliminary biological evaluation shows scope for potential applications.

GRAPHICAL ABSTRACT



ARTICLE HISTORY
Received 6 June 2018

KEYWORDS
L-(+)-lactic acid; chiral benzimidazole; morpholine; diastereoselective reductions; intramolecular cyclization

Introduction

Chiral benzimidazoles have attracted much attention due to ease of accessibility and proven applications in many areas of stereodiscriminations.[1,2] Additionally, many bioactive compounds of both natural and synthetic origin contain benzimidazole scaffolds as a core structural motif.[3] Our group has contributed to some of these applications in significant ways, including kinetic resolutions,[4] enantioselective synthesis,[5] and chiral molecular recognition.[6] Our research efforts in the last decade were focused on developing chiral benzimidazoles and their applications in chiral processes.[7–9]

Morpholines, in general, are derived from amino alcohols and amino acids and introduction of chiral center in morpholines is often inherited from the enantiopure amino alcohols and amino acids from the chiral pool.[10] Such an approach, however, is expensive and limits the number of chiral morpholines that can be accessed.

CONTACT Anil V. Karnik avkarnik@chem.mu.ac.in Department of Chemistry, University of Mumbai, Kalina, Santacruz (E), Mumbai 400098, India.

Supplemental data (full experimental detail, ^{1}H and ^{13}C NMR spectra, Mass spectra, and HPLC analysis) can be accessed on the publisher's website.

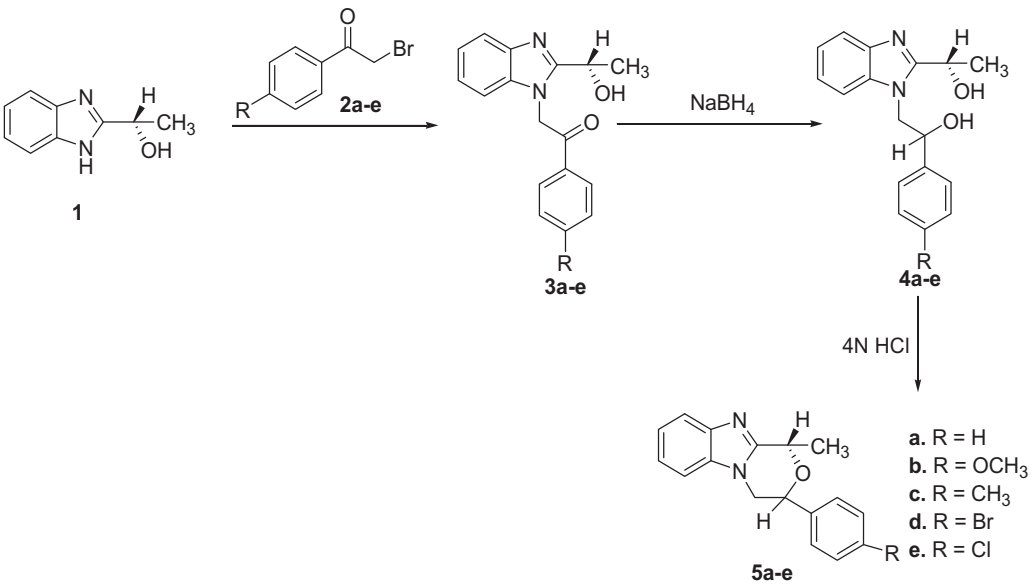
Chiral morpholines have been employed as versatile synthons for the syntheses of diversely substituted enantiopure amino acids,[11,12] amino alcohols,[13] and the total syntheses[14] of various natural products.[10] Morpholines have also found applications as catalysts and ligands in asymmetric addition of organo-zinc compounds to aldehydes, amides, and cyclization of enals with ketones, aldolization, indoles with unsaturated aldehydes, alkylation of Heck cross-coupling of aryl halides with alkenes, Michael addition of α,β-unsaturated aldehydes to 1,3-diketones, Buchwald–Hartwig amination of aryl chlorides.[15] Morpholines exhibit a wide range of bioactivities like anti-cancer,[16] anti-microbial,[17] anti-inflammatory,[18] antioxidants,[19] etc. Several drugs containing morpholine scaffold are marketed.[15] Morpholines, developed by Williams and coworkers, have been widely employed as chiral auxiliaries.[20]

Looking into our earlier accomplishments[21,22] of the compounds possessing (*S*)-(-)-2-(α-hydroxyethyl) benzimidazole scaffolds, we have envisioned that chiral benzimidazole fused morpholines could be potential candidates for chiral applications. Thus, it was decided to employ a chiral benzimidazole and an inexpensive phenacyl bromide, reacting in a controlled diasteroselective manner, to yield enantiomerically enriched morpholines.

Results and discussion

We utilized (*S*)-(-)-2-(α-hydroxyethyl)-benzimidazole **1** as an enantiopure precursor, which is obtained via Philips condensation[23] of (L)-(+)-lactic acid and *o*-phenylene diamine. Introduction of prochiral center on the benzimidazole **1** was achieved by alkylating it at the nitrogen atom with phenacyl bromide derivatives **2a–e** to afford alkylated product **3(a–e)**. The reduction of the alkylated compounds **3(a–e)** were carried out with sodium borohydride in methanol at 0 °C to yield **4(a–e)**. The acid catalyzed cyclization of the reduced products **4(a–e)** produced the desired cyclized morphilino benzimidazole derivatives **5(a–e)** (Scheme 1). The cyclization step involves protonation of the hydroxyl group along with generation of secondary carbocation followed by intramolecular attack of internal nucleophile resulting in formation of benzimidazole derived morpholines. All the target 2'-aryl-6'-methyl morpholino [4, 3-a] benzimidazoles (**5a–e)** were deduced by their spectral (^{1}H NMR, ^{13}C NMR, and DEPT) studies, and the stereochemical outcome of the diastereoselective reaction was determined using Chiral HPLC analyses.

The diastereomeric nature of the alkylated compound **3a** was confirmed using ^{1}H NMR and 13C NMR, wherein we could observe well distinguishable diastereomeric peaks for CH_3, CH_2, and CH protons (Figure 1) and carbons. The presence of carbonyl group was confirmed using 13C NMR, exhibited a signal at δ 192.17 ppm. DEPT spectrum displayed two negative diastereomeric peaks one at δ 49.87 and other at 52.17 indicating two types of methylene carbons in the analyte. The diastereomeric nature of the alkylated product was a bit of surprise for us as the alkylated compound has one chiral carbon. The diastereomeric nature can only be accounted for if the alkylated nitrogen of the benzimidazole ring acts as the other stereogenic center. The configurational stability of nitrogens at room temperature is rather low. The pyramidal inversion, responsible for poor configurational stability seems to be prevented, allowing the nitrogen to exhibit stereoisomerism. It can be proposed that the dissymmetric influence



Scheme 1. Preparation of chiral morpholino [4, 3-a] benzimidazole **(5a–e)**.

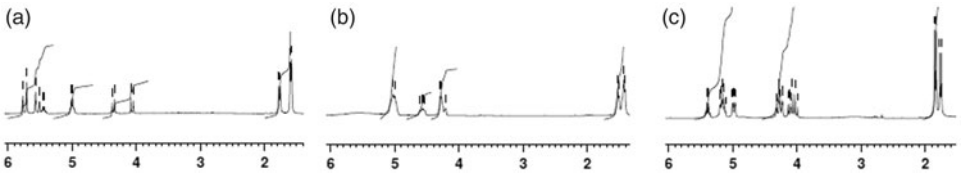
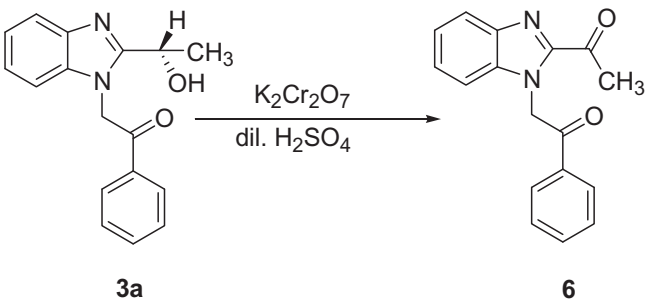


Figure 1. ^{1}H NMR spectra (a) for **3a**, (b) for **4a**, (c) for **5a**.

of the chiral carbon makes one of the configurational isomer, due to dissymmetry at nitrogen, more preferred and the molecule clearly exhibits diastereomeric pattern in ^{1}H NMR spectrum. The geminal coupling of CH_2 group clearly indicated that two protons existed in dissimilar environments. The mass spectrum showed m/z 280 molecular ion peak. It can be expected that a chiral center in close proximity to a prochiral reaction center should exhibit strong influence and should be able to exhibit diastereoselectivity. To confirm this aspect, we have oxidized[24] **3a** to **6** as shown in (Scheme 2). The compound **6** has been adequately characterized. The IR shows absence of hydroxyl group, the signal for carbonyl group appears as overlapped signal for two types of carbonyls, the ^{1}H NMR, ^{13}C NMR, and DEPT do not exhibit the diastereomeric nature. The mass spectrum confirmed the molecular weight and additionally exhibited m/e 43 peak and the corresponding m/e 235 signal due to the loss of acetyl group. Another important change is absence of 160 base peak seen in mass spectrum of **3a**. This can be due to the elimination of enolic acetophenone, formed via proton of hydroxyl group abstraction by the carbonyl group present in **3a**. The same carbonyl group is also present in compound **6**, but the base peak no longer is m/e 160. The removable hydrogen in the form of hydroxyl group is oxidized to carbonyl group in compound **6**.

The reduction of **3a** was also found to be a diastereoselective process with formation of another chiral center in the molecule leading to diol formation. Again, the NMR



3a 6

Scheme 2. Oxidation of (**3a**) gives compound (**6**).

signals for **4a** appear as diastereomeric, but only two diasteromeric signals are seen for each set of equivalent protons. The nitrogen behaves as a chiral center in **3a** and therefore after reduction step, with the introduction of one more chiral center, one could expect three diastereomeric signals for each set of equivalent protons; however, only two were seen in NMR spectra, both ^{1}H NMR and ^{13}C NMR. The ^{1}H NMR showed diastereotopic protons signals. One signal appeared as a doublet with $J = 5.7$ Hz, at δ 1.55 was diastereomeric with signal at δ 1.46 (Figure 1). The geminal coupling related to CH_2 protons was less pronounced in the reduced product. The presence of diastereomeric signal was confirmed using ^{13}C NMR. The disappearance of carbonyl group was clearly seen in ^{13}C NMR. Diastereomeric peaks were seen for methyl, methylene, and two methine group. The presence of diastereomeric peaks was also confirmed using DEPT showing two negative peaks one at δ 51.47 and other at 51.67 indicating two methylene carbons in the product. The mass spectrum showed m/z 282 molecular ion peak.

The ^{1}H NMR for **5a** showed diastereotopic protons signals. One signal appeared as a doublet with $J = 6.6$ Hz, at δ 1.85 was diastereomeric with signal at δ 1.75. The ^{1}H NMR clearly indicates that reaction had taken place in a highly diastereoselective manner (Figure 1). The presence of diastereomeric signal was confirmed using ^{13}C NMR. Diastereomeric peaks were seen for methyl, methylene, and two methine groups. The presence of diastereomeric peaks was also confirmed using DEPT showing two negative peaks one at δ 47.46 and other at 48.39 indicating two methylene carbons in the product. The mass spectrum showed m/z 264 molecular ion peak. The diastereomeric ratios of the product were further confirmed using Chiral HPLC method with diastereomeric excess up to 77.36%. Under the standard reaction conditions, the reactions scaled up to multigram quantities provided uniform results, indicating the practical usefulness of this method.

Antibacterial and antifungal activity of lactic acid benzimidazole derived morpholine

The antimicrobial activities of synthesized compounds were determined using broth microdilution method.[25–29] All synthesized compounds and standard drugs were assessed against two representatives of Gram-Negative and Gram-Positive bacterial strain, namely *Escherichia coli* (MTCC 443), *Pseudomonas aeruginosa* (MTCC 1688),

Table 1. Antibacterial and antifungal activity of compounds **5(a–e)**.

Minimum inhibitory concentration (MIC, μM)							
	Gram + ve bacteria		*Gram − ve bacteria*		Fungi		
Compound	*E. coli*	*P. aeruginosa*	*S. aureus*	*S. pyogenus*	*C. albicans*	*A. niger*	*A. clavatus*
5a	200	100	**250**	250	**500**	1000	500
5b	**62.5**	125	**100**	250	1000	1000	1000
5c	250	250	**250**	500	1000	250	250
5d	200	100	**250**	250	**500**	1000	1000
5e	**62.5**	100	**250**	100	1000	1000	1000
Standard drugs							
Ampicillin	**100**	–	**250**	**100**	–	–	–
Chloramphenicol	**50**	50	**50**	**50**	–	–	–
Nystatin	–	–	–	–	**100**	**100**	**100**
Griseofulvin	–	–	–	–	**500**	**100**	**100**

Staphylococcus aureus (MTCC 96), and *Streptococcus pyogenes* (MTCC 442) and three fungi, namely *Candida albicans* (MTCC 227), *Aspergillus niger* (MTCC 282), and *Aspergillus clavatus* (MTCC 1323). The strains employed for the activity were procured from Institute of Microbial Technology, Chandigarh (India). Mueller Hinton Broth was used as a nutrient medium and used to dilute the compound suspension for the test bacterial strain, whereas Sabouraud Dextrose Broth was used for fungal nutrition. Ampicillin, Chloramphenicol and Nystatin, Griseofulvin were used as reference standards for anti-bacterial and anti-fungal drugs, respectively. Bacterial strains were primarily inoculated into Mueller–Hinton agar for overnight growth. A number of colonies were directly suspended in saline solution until the turbidity matched the turbidity of McFarland standard (approximately 105 CFU mL^{-1}], i.e., inoculum size for test strain was adjusted to 105 CFU mL^{-1} (Colony Forming Unit per milliliter) per well by comparing the turbidity (turbidimetric method). Similarly, fungi were inoculated on Sabouraud Dextrose Broth, and the procedures of inoculum standardization were similar. DMSO was used as solvent to get the desired concentration of the synthesized compounds and standard drugs to test upon standard microbial strains. Each compound and standard drug was diluted obtaining 2000 μg/mL concentration, as a stock solution. By further progressive dilutions with test medium, the required concentrations were obtained for primary and secondary screening. In primary screening 0.2 mL of 1000, 500 and 250 μg/mL concentrations of the synthesized compounds were tested. The active compounds found in this primary screening were further diluted and 0.2 mL of 200, 100, 62.5, 50, 25, 12.5, and 6.25 μg/mL concentrations for secondary screenings to test against all microorganisms. Briefly, the control tube containing no antibiotic was immediately sub cultured (before inoculation) by spreading a loopful evenly over a quarter of plate of medium suitable for growth of tested organisms. The tubes were then put for incubation at 37 °C for 24 h for bacteria and 48 h for fungi. Growth or lack of growth in the tubes containing the antimicrobial agent was determined by comparison with the growth control, indicated by turbidity. The lowest concentration that completely inhibited visible growth of organism was recorded as the minimal inhibitory concentration (MIC, μg/mL), i.e., the amount of growth from the control tube before incubation (which represents the original inoculum) is compared. A set of tubes containing only seeded broth and the solvent controls were maintained under identical conditions so as to make sure that the solvent had no influence on strain growth.

The result of this is much affected by size of the inoculum. The interpretation of the results was based on the standard drugs used for bacterial and fungi strain, respectively. The results are summarized in Table 1 as minimal inhibitory concentration (MIC, μg/mL).

Antimicrobial activity of the synthesized compounds **5(a–e)** was determined using broth microdilution method as shown in Table 1. Compounds **5(a–e)** were found to be active against gram-positive as well as gram-negative strains. Compounds **5(a,c,d)** showed similar level of activity against *S. aureus*, in accordance with standard drug ampicillin. Compound **(5b)** showed higher activity than standard drug ampicillin against *E. coli* and *S. aureus*. Compound **(5e)** also showed higher activity than standard drug ampicillin against *E. coli* and a similar level of activity was seen in accordance with *S. aureus* and *S. pyogenes*. The antifungal activity test indicated that compounds **5(b,c,e)** are less active against all fungal strains in comparison with standard drugs. Compounds **(5a)** and **(5d)** were found to exhibit similar activity against *C. albicans* in comparison with Griseofulvin. Presence of electron donating groups like methyl, methoxy, chloro, bromo at position 4 of the aromatic ring seems to be important for antibacterial activity due to resonance effect.

Conclusion

An efficient methodology was developed for the synthesis of enantiomerically enriched morpholines. The method gives access to a series of benzimidazole fused morpholines containing two chiral centers in the morpholine ring structure in good yields (up to 60% yield) and moderate diastereoselectivity (up to 77.36%). Moreover, the current method provides a convenient approach for the facile incorporation of two biologically important scaffolds. The newly synthesized benzimidazole derived morpholines were screened for antimicrobial activity. Compound **(5b)** showed higher activity than standard drug ampicillin against *E. coli* and *S. aureus*.

Experimental

General experimental procedures

Synthesis of 2-[2-(1-hydroxyethyl)-benzoimidazol-1-yl]-1-phenyl ethanone)] (3a–e)

An equimolar proportion of (*S*)-(-)-2-(α-hydroxyethyl)-benzimidazole, 2 g (12.34 mmol) and Phenacyl bromide (12.34 mmol) were taken in DMF (15 mL) and reaction was carried out using 2.040 g (14.80 mmol) K_2CO_3 as a base. The reaction was found to be over in 6–8 h at room temperature when monitored with tlc. Purification of the product, obtained on aq. work up, was carried out with column chromatography. The eluent mixture was 80:20 (Chloroform:Pet Ether) which afforded pure white solid product.

2 -[2-(1-Hydroxyethyl)-benzoimidazol-1-]yl-1-phenyl ethanone (3a)

M.p. = 178–180 °C; Yield: 85%; IR (KBr, cm^{-1}): $\nu = 3220$, 3059, 2932, 1685, 1578, 1249, 1076, 986; ^1H NMR (300 MHz, $CDCl_3$, ppm): δ 7.16–6.98 (m, 2H; ArH), 7.25–7.19

(m, 2H; ArH), 7.50–7.39 (m, 1H; ArH), 7.70–7.53 (m, 2H; ArH), 8.00–7.76 (m, 2H; ArH), 5.77–5.51 (two doublets, $J = 18.3$ Hz; 2H; CH_2, coupled due to geminal coupling), 5.01–4.99 (q, $J = 6.6$ Hz, 1H;CH), 1.77–1.582 (two doublets for CH_3 attached to CH, $J = 6.6$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 19.22, 21.88, 49.88, 52.17, 64.46, 65.07, 94.63, 108.88, 109.04, 119.12, 119.67, 122.28, 122.39, 156.17, 192.17; Anal.calcd for $C_{17}H_{16}N_2O_2$ C, 72.85 H 5.75 N 10.01 found C 72.74; H 5.65; N 10.01; DEPT ^{135} (75 MHz, $CDCl_3$, ppm): Two negative peaks one at δ 49.87 and other at δ 52.17 indicating two methylene protons in compound; Mass Spectrum: Molecular ion m/z = 280. Optical Rotation: [α] $589^{25} = -130^\circ$ (c 1, MeOH).

Synthesis of 2-[2-(1-Hydroxyethyl) benzoimidazol-1-yl]-1-phenylethanol (4a–e)

The 2-[2-(1-hydroxyethyl)-benzoimidazol-1-yl]-1-phenyl ethanone (3.57 mmol) was taken in methanol and was treated with sodium borohydride (0.892 mmol) with external cooling. The reaction mixture was stirred for 3–4 h and then poured into ice cold water resulting in a white solid product which was filtered, washed, and dried.

2 -[2-(1-Hydroxyethyl) benzoimidazol-1-yl]-1-phenylethanol (4a)

M.p. = 108–112 °C;; Yield: 80%; IR (KBr, cm^{-1}): $\nu = 3291$, 3055, 2671, 1614,1495, 1330, 1068; ^{1}H NMR (300 MHz, $CDCl_3$, ppm): $\delta = 7.268$–7.231 (m, 2H; ArH), 7.37–7.273 (m, 2H; ArH), 7.429–7.378 (m, 2H; ArH), 7.501–7.45 (m, 1H; ArH), 7.72–7.769 (m, 2H; ArH), 5.205–5.114 (m, 1H; CH attached to CH_2 group) 5.009–4.961 (q, 1H; $J = 3.3$ Hz; CH), −4.2743.994 (m, 2H; CH_2 attached to CH group), 1.526–1.411 (two doublets for CH_3 attached to CH, $J = 6.6$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$, ppm): 20.49, 22.35, 51.48, 51.67, 61.62, 63.89, 71.63, 72.13, 109.65, 118.92, 122.35, 134.59, 141.41, 156.37, 156.71; Anal.calcd for $C_{17}H_{18}N_2O_2$ C, 72.34; H, 6.38; N 9.9 Found C, 72.42; H, 6.48; N 9.7; DEPT ^{135} (75 MHz, $CDCl_3$, ppm): Two negative peaks one at δ 51.47 and other at 51.67 indicating two methylene protons in the product; Mass Spectrum: Molecular ion m/z = 282. Optical Rotation: [α] $589^{25} = -107^\circ$ (c 1, MeOH)

Synthesis of 2′-aryl-6′-methyl morpholino [4, 3-a] benzimidazole (5a–e)

The 2-[2-(1-Hydroxyethyl)-benzoimidazol-1-yl]-1-phenylethanol (3.54 mmol) was taken in a round bottom flask and refluxed for 5–6 h in 4 N HCl. After complete disappearance of starting material on tlc, the reaction mixture was poured into ice cold water followed by neutralization using $NaHCO_3$ which afforded a sticky mass. The crude mass was subjected to column chromatography by taking eluent mixture as 90:10 ($CHCl_3$:$CH_3COOC_2H_5$) resulting in semisolid product.

2 ′-phenyl-6′-methyl morpholino [4, 3-a] Benzimidazole (5a)

M.p. = 56–60 °C, yield =60%; IR (KBr, cm^{-1}): $\nu = 3062$, 2981, 2206, 1616, 1519, 1474, 1109, 944 cm; ^{1}H NMR (300 MHz, $CDCl_3$, ppm): $\delta = 7.362$–7.196 (m, 7H; ArH), 7.742–7.373 (m, 2H; ArH), 7.429–7.378 (m, 2H; ArH), 7.501–7.45 (m, 1H; ArH),

7.72–7.769 (m, 2H; ArH), 5.205–5.114 (m, 1H; CH attached to CH_2 group) 5.009–4.961 (q, 1H; $J = 3.3$ Hz; CH), 4.274–3.994 (m, 2H; CH_2 attached to CH group), 1.853–1.752 (two doublets for CH_3 attached to CH, $J = 6.6$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$, ppm): 19.34, 19.50, 47.46, 48.40, 69.23, 69.71, 72.19, 75.63, 108.90, 119.45, 122.34, 126.11, 128.75, 134.05, 151.68. Anal.calcd for $C_{17}H_{16}N_2O$ C, 72.77 H 5.55 N 10.08 found C 72.74; H5.45;N10.05; DEPT ^{135} (75 MHz, $CDCl_3$, ppm): Two negative peaks one at δ 47.46 and other at 48.39 indicating two methylene protons in the product. Molecular ion m/z = 264. Chiral HPLC: Chiralcel OD column of diacel, Solvent system: IPA:Hexane, 15:85, Flow rate = 0.5 mL/min, $\lambda = 255$ nm, $t = 14.24$ min, $t = 19.39$ min. Optical Rotation: $[\alpha]\ 589^{25} = -40^{\circ}$ (c 1, MeOH).

Synthesis of 2-(2-Acetyl-1H-benzimidazol-1-yl)-1-phenylethanone 6

To a solution of **3a**, 1 g (3.57mmol) in dil H_2SO_4 (5% 10 mL) was added at room temperature a solution of $K_2Cr_2O_7$ 1.05 g (3.57mmol) in water (6 mL) and conc. H_2SO_4 (4 mL) in a dropwise fashion, over a period of 20 min. The reaction mixture was stirred vigorously during addition. The separated solid was filtered and washed with water (3 × 5 mL). The precipitate was stirred in water (10 mL) and treated very carefully with aq. NH_3 to a pH of 6.0–6.5. The suspension was stirred for 0.5 h and filtered. The residue was washed with water (3 × 5 mL) and dried to obtain **6**. The m.p. of the compound obtained was 166–168 °C.

IR (KBr, cm^{-1}): $\nu = 2939\ cm^{-1}$, $1683\ cm^{-1}$, $1613\ cm^{-1}$, $1595\ cm^{-1}$, $1480\ cm^{-1}$, $1449\ cm^{-1}$, $1397\ cm^{-1}$, $1356\ cm^{-1}$.

^1H NMR (300 MHz, $CDCl_3$, ppm):$\delta = 8.049$–7.934(m, 3H;3 Ar protons), 7.657–7.264(m, 6H;6 Ar protons) 6.024 (s, 2H; CH_2 group), 2.81 (s, for 3 H, CH_3group).

13C NMR (75 MHz, $CDCl_3$, ppm):27.750, 51.340, 9.962, 122.199, 123.965, 126.302, 128.053, 129.015, 134.159, 134.597, 136.685, 141.741, 146.035, 191.797, 193.600.

DEPT ^{135} (75 MHz, $CDCl_3$, ppm): One negative peaks at δ 51.45 indicating methylene proton in the product.

Mass Spectrum: Molecular ion m/z value of 278.

Acknowledgments

PKT is thankful to UGC-BSR, New Delhi for the JRF and SRF awards. Authors express sincere thanks to Dr. Dhanji P. Rajani, Microcare Laboratory, Surat, for availing the antimicrobial screening facilities for the compounds herein.

Supplementary data

Supplemental data (full experimental detail, ^1H and ^{13}C NMR spectra, Mass spectra, and HPLC analyses) can be accessed on the publisher's website.

References

[1] Khose, V. N.; John, M. E.; Pandey, A. D.; Karnik, A. V. *Tetrahedron: Asymmetry* **2017**, *28*, 1233–1289. DOI: 10.1016/j.tetasy.2017.09.001.

[2] Khose, V.; John, M.; Pandey, A.; Borovkov, V.; Karnik, A. *Symmetry* **2018**, *10*, 34. DOI: 10.3390/sym10020034.
[3] Jaouad, E. H.; Badr, A.; Adnane, B.; M'Hammed, A.; Jamal, T. *Res. J. Pharm. Tech*. **2014**, *7*, 481–488.
[4] Karnik, A. V.; Kamath, S. S. *J. Org. Chem*. **2007**, *72*, 7435–7438. DOI: 10.1021/jo070962p.
[5] Karnik, A. V.; Kamath, S. S. *Tetrahedron: Asymmetry* **2008**, *19*, 45–48. DOI: 10.1016/j.tetasy.2007.12.006.
[6] Pandey, A. D.; Hasan, M.; Pissurlenkar, R. S.; Karnik, A. V. *Chem. Plus. Chem*. **2015**, *80*, 475–479. DOI: 10.1002/cplu.201402141.
[7] Mirgane, N. A.; Karnik, A. V. *Green Chem. Lett. Rev*. **2011**, *4*, 269–272. DOI: 10.1080/17518253.2011.571715.
[8] Tawde, T. S.; Wagh, S. J.; Sapre, J. V.; Khose, V. N.; Badani, P. M.; Karnik, A. V. *Tetrahedron: Asymmetry* **2016**, *27*, 130–135. DOI: 10.1016/j.tetasy.2016.01.002.
[9] Wagh, S. J.; Tawde, T. S.; Sapre, J. V.; Khose, V. N.; Karnik, A. V. *Indian J. Chem*. **2016**., 55B, 707–712.
[10] Wijtmans, R.; Vink, M. K. S.; Schoemaker, H. E.; van Delft, F. L.; Blaauw, R. H.; Rutjes, F. P. J. T. *Synthesis* **2004**, *2004*, 641. DOI: 10.1055/s-2004-816003.
[11] Williams, R. M.; Zhai, D.; Sinclair, P. J. *J. Org. Chem*. **1986**, *51*, 5021. DOI: 10.1021/jo00375a055.
[12] Ramer, S. E.; Cheng, H.; Palcic, M. M.; Vederas, J. C. *J. Am. Chem. Soc*. **1988**, *110*, 8526. DOI: 10.1021/ja00233a032.
[13] Segat-Dioury, F.; Lingibé, O.; Graffe, B.; Sacquet, M.; Lhommet, G. *Tetrahedron* **2000**, *56*, 233. DOI: 10.1016/S0040-4020(99)00935-7.
[14] Myers, A. G.; Kung, D. W. *J. Am. Chem. Soc*. **1999**, *121*, 10828. DOI: 10.1021/ja993079k.
[15] Naim, M. J.; Alam, O.; Alam, M. J.; Alam, P.; Shrivastava, N. *Int. J. Pharm. Pharm. Sci*. **2015**, *3*, 40–45.
[16] Xiao-Meng, W.; Jing, X.; Min-Hang, X.; She-Min, L.; San-Qi, Z. *Bioorg. Med. Chem. Lett*. **2015**, *25*, 1730–1735. DOI: 10.1016/j.bmcl.2015.02.067.
[17] Denitsa, Y.; Lalka, D.; Emiliya, C.; Bozhanka, M.; Aleksandra, D.; Zaklina, S.; Andrija, S. *J. Mol. Str*. **2012**, *1016*, 147–154. DOI: 10.1016/j.molstruc.2012.02.057.
[18] Smelcerovic, A.; Rangelov, M.; Smelcerovic, Z.; Veljkovic, A.; Cherneva, E.; Yancheva, D.; Nikolic, G. M.; Petronijevic, Z.; Kocic, G. *Food Chem. Toxicol*. **2013**, *55*, 493–497. DOI: 10.1016/j.fct.2013.01.052.
[19] Eleni, M. L.; Alexios, N. M.; Anastasios, N.; Angeliki, P. K. *Bioorg. Med. Chem*. **2015**, *23*, 7015–7023. DOI: 10.1016/j.bmc.2015.09.034.
[20] Sinclair, P. J.; Zhai, D.; Reibenspies, J.; Williams, R. M. *J. Am. Chem. Soc*. **1986**, *108*, 1103. DOI: 10.1021/ja00265a053.
[21] Mirgane, N. A.; Karnik, A. V. *Chirality* **2011**, *23*, 404–407. DOI: 10.1002/chir.20942.
[22] Pandey, A. D.; Hasan, M.; Karnik, A. V. *Tetrahedron: Asymmetry* **2013**, *24*, 706–712. DOI: 10.1016/j.tetasy.2013.04.021.
[23] Phillips, M. A. *J. Chem. Soc*. **1928**, *0*, 2393–2399. DOI: 10.1039/JR9280002393.
[24] Kumar, P. K.; Dubey, P. K. *Der. Pharma. Chem*. **2012**, *4*, 1292–1295.
[25] Isenberg, H. D. *Clinical Microbiology Handbook*, 2nd ed.; ASM Press: Washington DC, **2004**; Vol. *II*, Chapter 5, pp. 5.0.1.
[26] Desai, N. C.; Shihora, P. N.; Moradia, D. L. *Indian J. Chem*. **2007**, 46B, 550.
[27] National Committee for Clinical Laboratory Standards. *Methods for Dilution, Antimicrobial Susceptibility Tests for Bacteria that grow Aerobically Approved Standard, (M 7A5)*, 5th ed; Wayne, PA, **2000**.
[28] Shadomy, S. *In Manual of Clinical Microbiology*; Albert, B., Ed.; ASM Press: Washington, DC, **1991**; pp. 1173.
[29] Rattan, A. *Antimicrobials in Laboratory Medicine*; BI Churchill Livingstone: India, **2000**; pp. 85.