Article

An Efficient Synthesis of 2-Substituted Benzimidazoles via Photocatalytic Condensation of o-Phenylenediamine and Aldehydes

Jeshma Kovvuri, Burri Nagaraju, Ahmed Kamal, and Ajay Kumar Srivastava

ACS Comb. Sci., **Just Accepted Manuscript** • DOI: 10.1021/acscombsci.6b00107 • Publication Date (Web): 15 Sep 2016

An Efficient Synthesis of 2-Substituted Benzimidazoles via Photocatalytic Condensation of *o*-phenylenediamine and Aldehydes

Jeshma Kovvuri[†,‡], *Burri Nagaraju*[†,‡], *Ahmed Kamal**[†,‡§] *and Ajay K. Srivastava**[†,‡]

[†]Academy of Scientific and Innovative Research (AcSIR), New Delhi-110025, India

[‡]Medicinal Chemistry and Pharmacology Division, CSIR-Indian Institute of Chemical Technology, Hyderabad-500007, India

[§]Catalytic Chemistry Chair, Chemistry Department College of Science, King Saud University, Riyadh, Saudi Arabia

KEYWORDS: Benzimidazole, Photocatalytic condensation, Rose Bengal, *o*-phenylenediamine

ABSTRACT

A photocatalytic method has been developed for the efficient synthesis of functionalized benzimidazoles. This protocol involves photocatalytic condensation of *o*-phenylenediamines with various aldehydes using the Rose Bengal as photocatalyst. The method was found to be general and was successfully employed for accessing pharmaceutically important benzimidazoles by the condensation of aromatic, heteroaromatic and aliphatic aldehydes with *o*-

phenylenediamines, in good-to-excellent yields. Notably, the method was found to be effective for the condensation of less reactive heterocyclic aldehydes with *o*-phenylenediamines.

INTRODUCTION

The benzofused nitrogen containing heterocyclic compounds have a great importance in drug discovery, among them benzimidazole scaffold is of particular interest and has been categorized as a privileged scaffold.[1] The benzimidazole moiety is structurally correlated to the purine bases and is profusely found in a variety of natural products including vitamin B_{12}.[2] Several benzimidazole derivatives exhibit diversified pharmaceutical properties such as antimicrobial,[3] anticancer,[4] antiviral,[5] antihelmintic,[6] antioxidant,[7] antiulcer,[8] antihypertensive[9] and antitubercular.[10] For example, benzimidazoloquinolinone conjugate 'Dovitinib(**I**)', a potent EGFR-3 inhibitor, is currently in phase-III clinical trials for the treatment of metastatic renal cell cancer,[11] the thiazolobenzimidazole derivative 'Tiabendazole (**II**)' acts as an anthelmintic drug[12] and Pimobendan (**III**) has been used as a vasodilator for the management of heart failure in dogs[13](Figure 1). Additionally, the bisbenzimidazole containing Hoechst stain (**IV**) is widely used to stain DNA in fluorescence microscopy, immunohistochemistry and flow cytometry (Figure 1).[14]

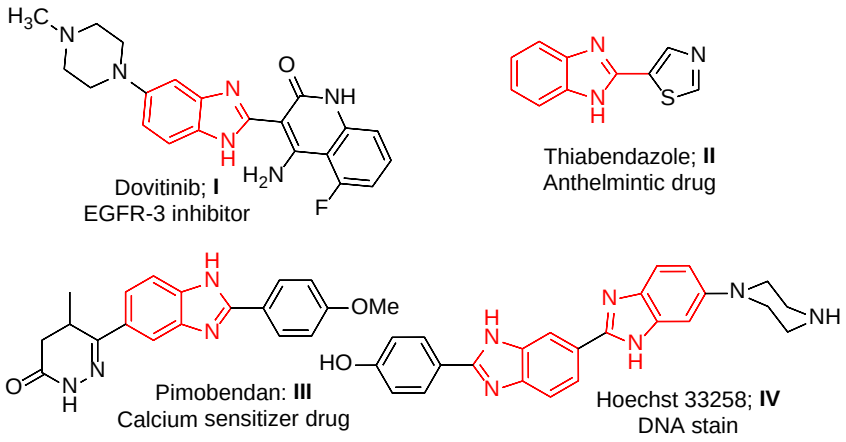
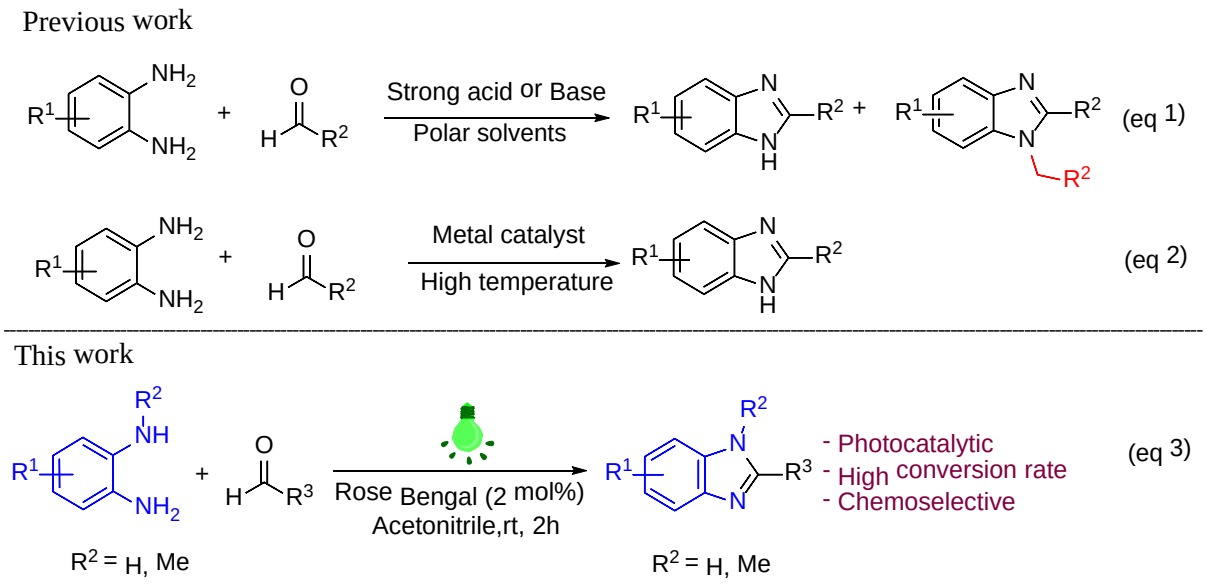


Figure1. Representative examples of benzimidazole containing important molecules

Owing to the vast importance of benzimidazoles in drug discovery, enormous efforts have been made to develop operationally simple synthetic methods for the construction of benzimidazole derivatives.[15] Usually, the condensation of *o*-phenylenediamines with aldehydes in the presence of acid,[16] base[17] or metal catalyst[18] produces benzimidazoles. The other methods include condensation of *o*-phenylenediamines with carboxylic acids, nitriles and *ortho*-esters under dehydrating conditions.[19] The dehydration of *N*-acylated *o*-phenylenediamines by using acetic acid,[19c-e] *p*-TSA[19f] or Amberlyst-15[19g] also produces benzimidazoles. Recently, a flow chemistry protocol has been developed to synthesize benzimidazoles by the condensation of *o*-phenylenediamines with aldehydes.[20] Though the reported methods are efficient and widely used, they possess several limitations such as the condensation of *o*-phenylenediamine and aldehyde in the presence of acid or base requires longer reaction times and produces *N1*-benzylated benzimidazole as an undesirable side product that is often very difficult to separate (Scheme 1, eq 1).[21] The metal catalyzed condensations require high temperature and the residual contamination of metal with the product might cause toxicity at the later stage of pharmaceutical applications (Scheme 1, eq 2).[22] Therefore, a mild, efficient and environment friendly method for the synthesis of benzimidazoles is of high importance. Considering the benefits of recently developed photocatalytic condensations under visible light,[23] we envisioned to explore the photocatalytic condensation of *o*-phenylenediamines with heteroaromatic aldehydes to synthesize pharmaceutically important benzimidazoles.[24] Herein, we report a photocatalytic method for the synthesis of benzimidazoles by the condensation of *o*-phenylenediamines with aldehydes (Scheme 1, eq 3).



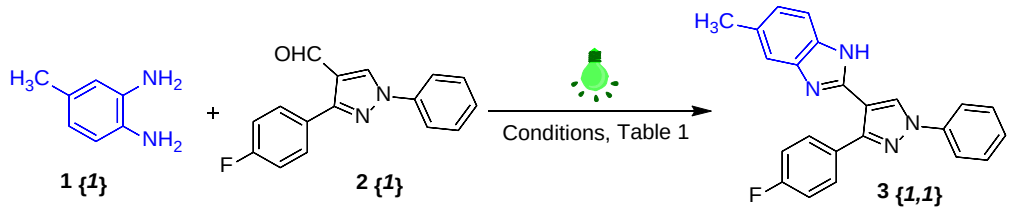
Scheme 1. Condensation of *o*-phenylenediamines and aldehydes for the synthesis of benzimidazoles

RESULTS AND DISCUSSION

Initially, we intended to utilize the reported method by Cho *et al*[25] for the photocatalytic condensation of *o*-phenylenediamine and pyrazolocarboxaldehyde to obtain the pyrazolobenzimidazole analogues as they exhibit excellent anticancer properties.[24] Our initial results showed that the method was not suitable for the heterocyclic aldehydes such as pyrazolocarboxaldehyde **2**{*1*} as the desired 2-pyrazolobenzimidazole **3**{*1,1*} was obtained in very poor yield in absence of photocatalyst (entry 1, Table 1). Change of solvent from methanol to water or acetonitrile did not improve the yield (entries 2-3, Table 1). Therefore, in order to facilitate the condensation, we decided to screen the organic photocatalysts such as Methylene Blue, Eosin Y, Rhodamine B and Rose Bengal (RB) under various reaction conditions (entries 4-7, Table 1) along with the ruthenium-based photocatalyst $Ru(bpy)_3(PF_6)_2$ (Entry 8, Table 1).

To our delight, addition of the photocatalyst significantly improved the yield of desired pyrazolobenzimidazole **3**{*1,1*}. Among the four organic photocatalysts screened, Rose Bengal (RB) gave the best yield when the reaction was performed in acetonitrile with 2 mol% of catalyst loading (entries 6 and 9-12, 14-16, Table 1). Efforts were also made to perform the condensation in environment friendly solvents such as water and ethanol (Entries 9, 12-13, Table 1). However, moderate yields were obtained in these solvents. Poor yields were observed in the absence of light and under the anaerobic conditions (entries 17-20, Table 1).

Table 1. Optimization of the Reaction Conditions:



Entry	Solvent	T (°C)/ *t*(h)	Visible light	Photocatalyst	Yield[a](%)
1.	Methanol	rt/12	+	--	12
2.	Water	rt/12	+	--	10
3.	Acetonitrile	rt/12	+	--	15
4.	Acetonitrile	rt/2	+	Methylene Blue[b]	63
5.	Acetonitrile	rt/2	+	Eosin Y[b]	55
6.	**Acetonitrile**	**rt/2**	**+**	**Rose Bengal[b]**	**90**
7.	Acetonitrile	rt/2	+	Rhodamine B[b]	81
8.	Acetonitrile	rt/2	+	$Ru(bpy)_3(PF_6)_2$[b]	80
9.	Water	rt/2	+	Rose Bengal[b]	50
10.	DCM	rt/2	+	Rose Bengal[b]	46

11.	Methanol	rt/2	+	Rose Bengal[b]	55
12.	Ethanol	rt/2	+	Rose Bengal[b]	60
13.	Ethanol	rt/2	+	Rhodamine B[b]	65
14.	Acetonitrile	rt/2	+	Rose Bengal[c]	72
15.	Acetonitrile	rt/2	+	Rose Bengal[d]	81
16.	Acetonitrile	rt/2	+	Rose Bengal[e]	89
17.	Acetonitrile	45°C /6	Dark	Rose Bengal[b]	18
18.	Acetonitrile	rt/12	Dark	Rose Bengal[b]	5
19.	Acetonitrile	rt/12	+	Rose Bengal[f]	10
20.	Methanol	rt/12	+	Rose Bengal[f]	5

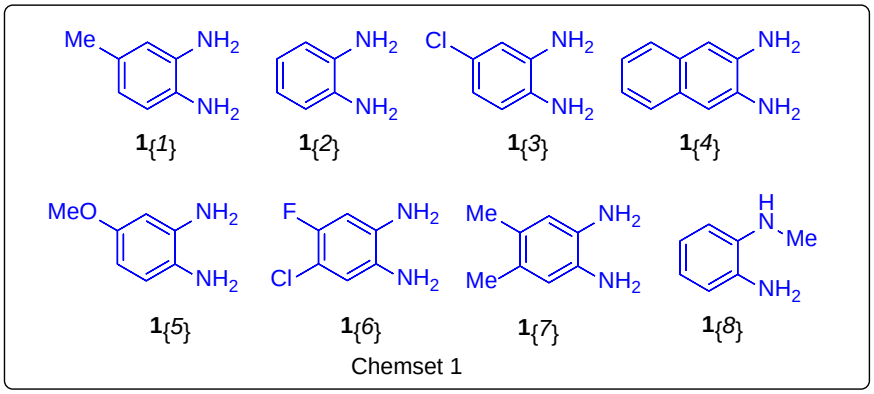
[a]Isolated yields,[b]Reactions were tried with 2 mol% of the catalyst, [c]0.5%of RB, [d]1 mol %of RB, [e]3 mol % of RB, [f]Inert atmosphere (under argon)

One of the most significant advantages with Rose Bengal is it's reusability without losing its catalytic potential.[26] Therefore, in order to check the recovery and reusability of the Rose Bengal in this condensation process, we recovered the catalyst during column purification of the product **3**{*1,1*} and reused it for the same condensation (Table 2). The recovered catalyst could be reused up to three cycles with almost similar catalytic activity as shown in table 2. The slight decrease in the yields might be associated with the uncharacterized impurities in the recovered catalyst.

Table 2. Yields of the product with 3 cycles of the catalyst

Entry	Reaction cycle	Yield (%)
1	Fresh run	90
2	1st cycle	88
3	2nd cycle	84
4	3rd cycle	81

With the optimized conditions in hand, we evaluated the reactions of substituted *o*-phenylenediamines with a variety of heterocyclic aldehydes such as substituted pyrazolocarboxaldehyde (**2**{*1*}-**2**{*3*}), *β*-carbolinecarboxaldehyde (**2**{*4*}), indole-3-carboxaldehydes (**2**{*5*}, **2**{*6*}), imidazothiazole-4-carboxaldehydes (**2**{*7*}, **2**{*8*}), propanal (**2**{*9*}), 3-phenylpropanaldehyde (**2**{*10*}), quinolinecarboxaldehydes (**2**{*11*}, **2**{*12*}), chromonecarboxaldehyde (**2**{*13*}), furfural (**2**{*14*}), imidazole carboxaldehyde (**2**{*15*}) and substituted benzaldehydes (**2**{*16*}-**2**{*21*}). Among these aldehydes aromatic and heteroaromatic aldehydes gave better yields than aliphatic aldehydes (Figure 2 and 3). Interestingly, the procedure was highly functional group tolerant and worked well with electron rich and electron deficient substrates (Figure 3). Further, to check the compatibility of this protocol with *N*-alkyl *o*-phenylenediamines, the condensation between *N*-Methyl-*o*-phenylenediamine and propanal was studied with the optimized reaction conditions that yielded the desired product **3**{*8, 9*} in 69 % yield (Figure 2 and 3). All the synthesized benzimidazoles were characterized by ^{1}H &^{13}C NMR, and HRMS spectral analysis.



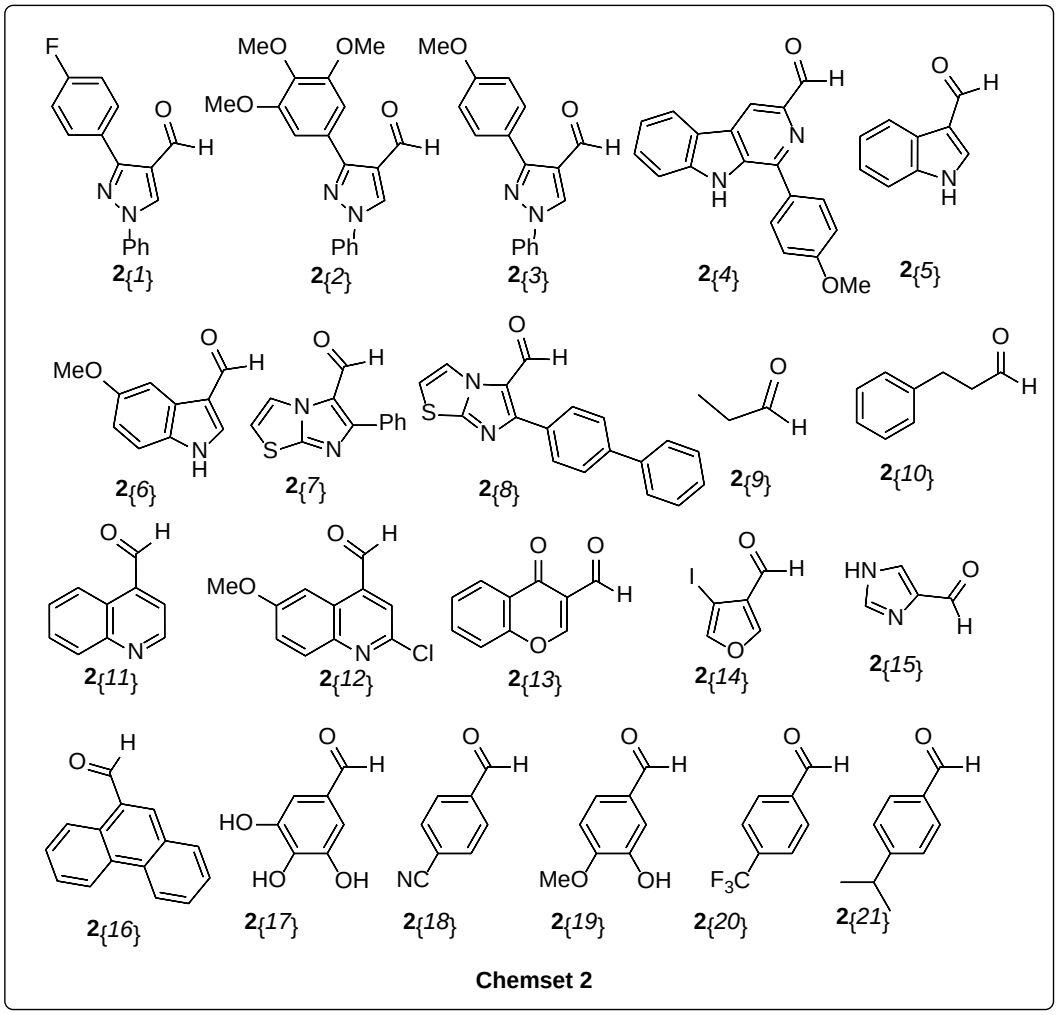


Figure 2: Chemsets; *o*-phenylenediamines **Chemset 1**; Aldehydes **Chemset 2**.

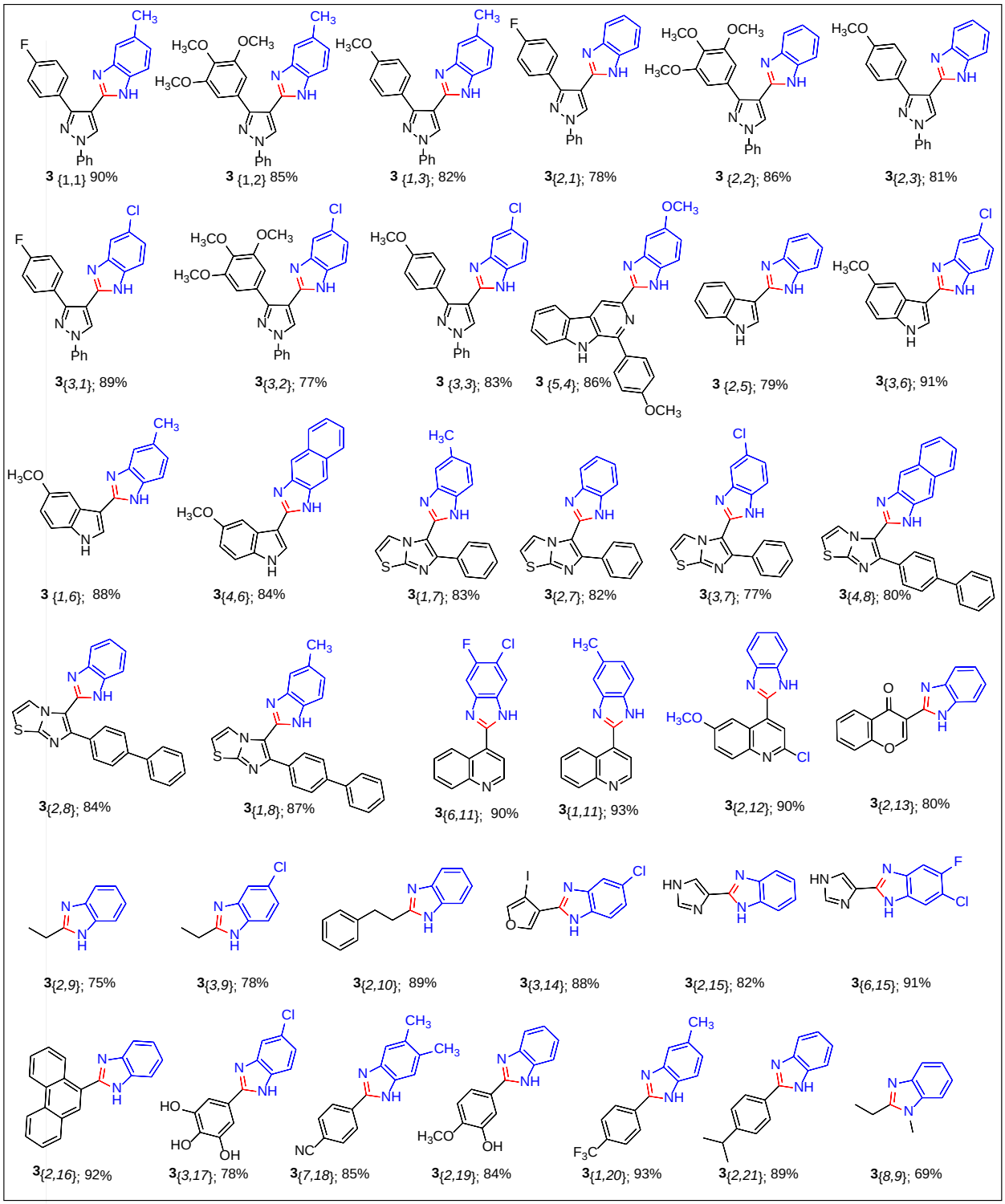


Figure 3. Synthesized benzimidazoles

A plausible mechanism for the condensation of *o*-phenylenediamine with aldehyde to afford 2-substituted benzimidazole, using Rose Bengal as a photocatalyst in the presence of visible light, has been outlined in the Figure 4.

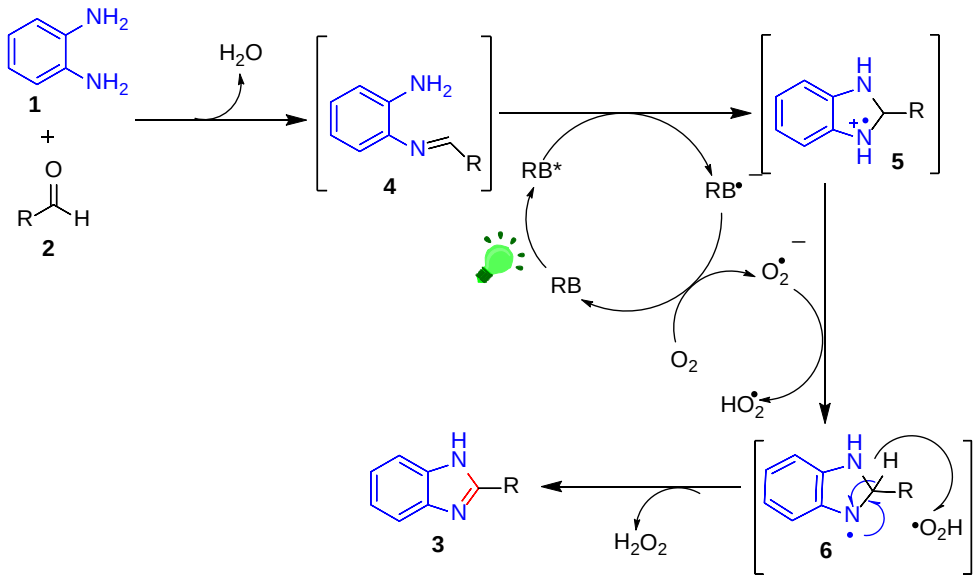


Figure4. Plausible mechanism

Imine**,** (**4**) is formed from the condensation between **1** and **2**. RB,* the excited state of RB, generated under visible light irradiation, is able to abstract an electron from imine *via* a single electron transfer (SET) process.[27] The photo-redox cycle is completed by the oxidation of the RB radical anion back to the ground state RB by dioxygen. The imine radical cation (**5**) donates one hydrogen atom to the dioxygen radical anion and results in the formation of **6** and hydrogen abstraction by hydroperoxyl radical (HOO·) results in the formation of desired product.

CONCLUSION

In summary, we have developed a robust, operationally simple and extremely general method for the synthesis of functionalized benzimidazoles by the photocatalytic condensation of *o*-phenylenediamines and aldehydes in metal-free conditions. The method does not require any

harsh reaction condition and can be used with the sensitive substrates. The procedure was found to be suitable for the condensations of relatively unreactive electron rich aldehydes such as substituted pyrazolo-, *β*-carboline-, imidazothiazolo-, quinoline-, chromone and indole-carboxaldehydes with *o*-phenylenediamines to obtain pharmaceutically important benzimidazoles.

EXPERIMENTAL SECTION

General Information

All chemicals, reagents and photocatalysts were purchased from the commercial sources and were used without further purification. Reactions were monitored by TLC on silica gel glass plate containing 60 GF-254, and visualization was done by UV light and iodine vapor. ^{1}H and ^{13}C NMR spectra were recorded on Bruker UXNMR/XWIN-NMR (300 MHz) or InovaVarian-VXR-unity (400, 500 MHz) instruments. Chemical shifts were expressed in parts per million (δ in ppm) downfield from TMS expressed as internal standard and coupling constants are expressed in Hz. ^{1}H NMR spectral data were reported in the following order: multiplicity (s, singlet; brs, broad singlet; d, doublet; dd, doublet of doublets; t, triplet; m, multiplet), coupling constants in Hz, and number of protons. ESI mass spectra were recorded on a Micromass Quattro LC using ESI+ software with capillary voltage 3.98 kV and an ESI mode positive ion trap detector. High resolution mass spectra were recorded on a QSTAR XL Hybrid MS-MS mass spectrometer. Melting points were determined with an electro thermal digitalmelting point apparatus IA9100 and are uncorrected. All the reactions were performed one by one in borosilicate glass vials using following general procedure and setup.

General Procedure for the synthesis of 2-substituted benzimidazoles: In a 30 ml clear glass vial charged with magnetic bead, aldehyde (1.0 mmol), *o*-phenylenediamine (1.0 mmol),

acetonitrile (10mL) and 2 mol % of Rose Bengal were taken. The reaction mixture was placed beside the 11 Watt LED bulb (the reaction also worked well with 5 or 7 Watt LED bulbs) in photochemical reactor box, open air and stirred until the complete consumption of starting materials observed on TLC analysis. After completion of the reaction, solvent was evaporated under vacuum and the residue was purified by the column chromatography by using hexane/ethylacetate as eluent to afford the final product. After isolation of the product, Rose Bengal was eluted by using chloroform/methanol that can be reused after evaporation of solvent under vacuum.

5-methyl-2-(3-(4-fluorophenyl)-1-phenyl-1H-pyrazol-4-yl)-1H-benzo[d]imidazole[**3**{*1,1*}]

Light brown solid; yield 90% (124.5 mg); mp 187-189 ˚C; ^{1}H NMR (300 MHz, $CDCl_3$+DMSO-d6) δ 8.65 (s, 1H), 7.86 (dd, *J* = 8.3, 5.6 Hz, 2H), 7.80 (d, *J* = 7.8 Hz, 2H), 7.53 – 7.41 (m, 3H), 7.34 (t, *J* = 7.1 Hz, 2H), 7.05 (dd, *J* = 11.6, 5.4 Hz, 3H), 2.47 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$+DMSO-d6) δ 161.50 (d, *J* = 246.9 Hz), 148.66, 144.13, 138.08, 137.18, 136.05, 130.70, 129.18, 129.08, 128.36, 127.53, 125.77, 122.58, 117.56, 114.01, 113.72, 113.07, 111.33, 20.44; HRMS (ESI) : calcd for $C_{23}H_{18}N_4F$ $[M+H]^+$ 369.1505, found 369.1510.

ASSOCIATED CONTENT

Supporting Information

Characterization data, Copies of ^{1}H &^{13}C NMR, and HRMS Spectra of all the synthesized compounds**.**"This material is available free of charge via the Internet at http://pubs.acs.org."

AUTHOR INFORMATION

Corresponding Author

*Email: aksrivastava@iict.res.in; Contact No: +91-40-2719-1646

Author Contributions

The manuscript was written through contributions of all the authors. All authors have given approval to the final version of the manuscript.

Funding Sources

This work was supported by DST-INSPIRE, New Delhi and Council of Scientific & Industrial Research (CSIR), New Delhi under the XIIth Five Year Plan Project 'Affordable Cancer Therapeutics (ACT)' [Grant No. CSC0301]

Notes

Any additional relevant notes should be placed here.

ACKNOWLEDGMENTS

The authors JK and BN thankful to Department of Science & Technology, New Delhi for providing fellowships under DST-INSPIRE programme.

ABBREVIATIONS

RTK, receptor tyrosine kinase; LED, light emitting diode; RB, rose Bengal; SET, single electron transfer; DCM, dichloromethane; TLC, thin layer chromatography.

REFERENCES

1. Welsch, M. E.; Snyder, S. A.; Stockwell, B. R. Privileged Scaffolds for Library Design and Drug Discovery. *Curr. Opin. Chem. Biol.* **2010**, *14*, 347.

2. (a) Bansal, Y.; Silakari, O. The therapeutic journey of benzimidazoles. *Bioorg. Med. Chem.* **2012**, *20,* 6208. (b) Fang, X.-J.; Jeyakkumar, P.; Avula, S. R.; Zhou, Q.; Zhou, C.-H. Design, synthesis and biological evaluation of 5-fluorouracil-derived benzimidazoles as novel type of potential antimicrobial agents. *Bioorg. Med. Chem. Lett.* **2016**, *26,* 2584. (c) Kamal, A.; Rao, M. P. N.; Swapna, P.; Srinivasulu, V.; Bagul, C.; Shaik, A. B.; Mullagiri, K.; Kovvuri, J.; Reddy, V. S.; Vidyasagar, K.; Nagesh, N. Synthesis of β-carboline-benzimidazole conjugates using lanthanum nitrate as a catalyst and their biological evaluation. *Org. Biomol. Chem.* **2014**, *12,* 2370.

3. (a) Hernandez-Luis, F.; Hernandez-Campos, A.; Castillo, R.; Navarrete-Vazquez, G.; Soria-Arteche, O.; Hernandez-Hernandez, M.; Yepez-Mulia, L. Synthesis and biological activity of 2-(trifluoromethyl)-*1H*-benzimidazole derivatives against some protozoa and Tricheinellaspiralis. *Eur. J. Med. Chem.* **2010,** *45,* 3135. (b) Khalil, A.M.; Berghot, M. A.; Gouda, M.A. Synthesis and study of some new 1,3-isoinodoledione derivatives as potential antibacterial agents. *Eur. J. Med. Chem.* **2010,** *45,* 1552. (c) Goker, H.; Boykin, D. W.; Yildiz, S. Synthesis and potential antimicrobial activity of some novel 2-phenyl or methyl-4H-1-benzopyran-4-one carrying amidinobenzimidazoles. *Bioorg. Med. Chem.* **2005,** *13,* 1707.

4. (a) Kamal, A.; Ponnampalli, S.; Vishnuvardhan, M. V. P. S.; Rao, M. P. N.; Mullagiri, K.; Nayak, V. L.; Chandrakant, B. Synthesis of imidazothiadiazole-benzimidazole conjugates as mitochondrial apoptosis inducers. *Med. Chem. Commun.* **2014**, *5,* 1644. (b) Saour, K.; Lafta, D. Synthesis of New Benzimidazoles and Benzothiazole Disulfide Metal Complexes as G-quadruplex Binding Ligands**.** *Anticancer Agents Med. Chem.* ***2016****, 16,* 891. (c) Kim, M. K.; Shin, H.; Park, K.-s.; Kim, H.; Park, J.; Kim, K.; Nam, J.;

Choo, H.; Chong, Y. Benzimidazole Derivatives as Potent JAK1-Selective Inhibitors. *J. Med. Chem.* **2015**, *58,* 7596.

5. (a) Zou, R.; Ayres, K. R.; Drach, J. C.; Townsend, L. B. Synthesis and Antiviral Evaluation of Certain Disubstituted Benzimidazole Ribonucleosides. *J. Med. Chem.* **1996,** *39*, 3477. (b) Li, Y.-F.; Wang, G.-F.; He, P.-L.; Huang, W.-G.; Zhu, F.-H.; Gao, H.-Y.; Tang, W.; Luo, Y.; Feng, C.-L.; Shi, L.-P.; Ren, Y.-D.; Lu, W.; Zuo, J.-P. Synthesis and Anti-Hepatitis B Virus Activity of Novel Benzimidazole Derivatives. *J. Med. Chem.* **2006,** *49,* 4790.
6. Chassaing, C.; Berger, M.; Heckeroth, A.; Ilg, T.; Jaeger, M.; Kern, C.; Schmid, K.; Uphoff, M. Highly Water-Soluble Prodrugs of Anthelmintic Benzimidazole Carbamates: Synthesis, Pharmacodynamics, and Pharmacokinetics. *J. Med. Chem.* **2008,** *51*, 5.
7. (a) Mavrova, A. T.; Yancheva, D.; Anastassova, N.; Anichina, K.; Zvezdanovic, J.; Djordjevic, A.; Markovic, D.; Smelcerovic, A. Synthesis, electronic properties, antioxidant and antibacterial activity of some new benzimidazoles. *Bioorg. Med. Chem*. **2015**, *23*, 6317. (b) Holloway, G. A.; Baell, J. B.; Fairlamb, A. H.; Novello, P. M.; Parisot, J. P.; Richardson, J.; Watsona, K. G.; Street, I. P. Discovery of 2-iminobenzimidazoles as a new class of trypanothionereductase inhibitor by high-throughput screening. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 1422.
8. Cereda, E.; Turconi, M.; Ezhaya, A.; Bellora, E.; Brambilla, A.; Pagani, F.; Donetti A. Anti-secretory and ‘anti-ulcer activities of some new 2-(2-pyridylmethyl-sulfinyl)-benzimidazoles. *Eur. J. Med. Chem.* **1987**, *22,* 527.

9. Wang, J.-L.; Zhang, J.; Zhou, Z.-M.; Li, Z.-H.; Xue, W.-Z.; Xua, D.; Hao, L.-P.; Han, X.-F.; Fei, F.; Liu, T.; Liang, A.-H. Design, synthesis and biological evaluation of 6-substituted aminocarbonyl benzimidazole derivatives as nonpeptidic angiotensin II AT_1 receptor antagonists. *Eur. J. Med. Chem.* **2012**, *49*, 183.

10. (a) Hameed, S. P.; Raichurkar, A.; Madhavapeddi, P.; Menasinakai, S.; Sharma, S.; Kaur, P.; Nandishaiah, R.; Panduga, V.; Reddy, J.; Sambandamurthy, V. K.; Sriram, D. Benzimidazoles: Novel Mycobacterial Gyrase Inhibitors from Scaffold Morphing. *ACS Med. Chem. Lett.* **2014**, *5*, 820. (b) Park, B.; Awasthi, D.; Chowdhury, S. R.; Melief, E. H.; Kumar, K.; Knudson, S. E.; Slayden, R. A.; Ojima, I. Design, synthesis and evaluation of novel 2,5,6-trisubstituted benzimidazoles targeting FtsZ as antitubercular agent. *Bioorg. Med. Chem.* **2014,** *22*, 2602.

11. Renhowe, P. A.; Pecchi, S.; Shafer, C. M.; Machajewski, T. D.; Jazan, E. M.; Taylor, C.; Antonios-McCrea, W.; McBride, C. M.; Frazier, K.; Wiesmann, M.; Lapointe, G. R.; Feucht, P. H.; Warne, R. L.; Heise, C. C.; Menezes, D.; Aardalen, K.; Ye, H.; He, M.; Le, V.; Vora, J.; Jansen, J. M.; Wernette-Hammond, M. E.; Harris, A. L. Design, structure-activity relationships and in vivo characterization of 4-amino-3-benzimidazol-2-ylhydroquinolin-2-ones: A Novel Class of Receptor Tyrosine Kinase Inhibitors. *J. Med. Chem.* **2009**, *52*, 278.

12. (a) Goodman and Gilman's The Pharmacological Basis of Therapeutics. 8th ed. Gilman, A. G.; Rall, T.W.; Nies, A.S.; Taylor, P. eds. New York, NY. Pergamon Press, **1990**, 970. (b) Zhang, C.; Zhong, B.; Yang, S.; Pan, L.; Yu, S.; Li, Z.; Li, S.; Su, B.; Meng, X. Synthesis and biological evaluation of thiabendazole derivatives as anti-angiogenesis and vascular disrupting agents. *Bioorg. Med. Chem*. **2015**, *23*, 3774.

13. (a) Verdouw, P. D.; Hartog, J. M.; Duncker, D. J.; Roth, W.; Saxena, P. R. Cardiovascular profile of pimobendan, a benzimidazole-pyridazinone derivative with vasodilating and inotropic properties. *Eur. J. Pharmacol.* **1986**, *126,* 21. (b) Hata, K.; Goto, Y.; Futaki, S.; Ohgoshi, Y.; Yaku, H.; Kawaguchi, O.; Takasago, T.; Saeki, A.; Taylor, T. W.; Nishioka, T. Mechanoenergetic effects of pimobendan in canine left ventricles. Comparison with dobutamine. *Circulation* **1992**, *86,* 1291. (c) Hanzlicek, A. S.; Gehring, R.; KuKanich, B.; KuKanich, K. S.; Borgarelli, M.; Smee, N.; Olson, E. E.; Margiocco, M. Pharmacokinatics of oral pimobendan in healthy cats. *J. Vet. Cardiol.* **2012**, *14*, 489.

14. (a) Mocharla, R.; Mocharla, H.; Hodes, M. E. A novel, sensitive fluorometric staining technique for the detection of DNA in RNA preparations. *Nucl. Acids Res.* **1987**, *15,* 10589. (b) Kubbies, M. Flow cytometric recognition of clastogen induced chromatin damage in G0/G1 lymphocytes by non-stoichiometric Hoechst fluorochrome binding. *Cytometry* **1990**, *11*, 386. (c) Sterzel, W.; Bedford, P.; Eisenbrand, G. Automated determination of DNA using the fluorochrome Hoechst 33258. *Anal. Biochem.* **1985**, *147*, 462.

15. (a) Preston, P. N. Synthesis, reactions, and spectroscopic properties of benzimidazoles. *Chem. Rev.* **1974**, *74,* 279. (b) Horton, D. A.; Bourne, G. T.; Smythe, M. L. The Combinatorial Synthesis of Bicyclic Privileged Structures of Privileged Substructures. *Chem. Rev.* **2003**, *103*, 893.

16. (a) Zhang, Z.-H.; Yin, L.; Wang, Y.-M. An expeditious synthesis of benzimidazoles derivatives catalyzed by Lewis acids. *Catal. Commun.* **2007**, *8*, 1126. (b) Kommi, D. N.; Kumar, D.; Bansal, R.; Chebolu, R.; Chakraborti, A. K. “All-water” chemistry of

tandem N-alkylation–reduction–condensation for synthesis of *N*-arylmethyl-2-substituted benzimidazoles. *Green Chem.* **2012**, *14,* 3329. (c) Bressi, J. C.; Jong, R. d.; Wu, Y.; Jennings, A. J.; Brown, J. W.; O'Connell, S.; Tari, L. W.; Skene, R. J.; Vu, P.; Navre, M.; Cao, X.; Gangloff, A. R. Benzimidazole and imidazole inhibitors of histone deacetylases: Synthesis and biological activity. *Bioorg. Med. Chem. Lett*. **2010**, *20,* 3138. (d) Ishikawa, M.; Nonoshita, K.; Ogino, Y.; Nagae, Y.; Tsukahara, D.; Hosaka, H.; Maruki, H.; Ohyama, S.; Yoshimoto, R; Sasaki, K.; Nagata, Y.; Eiki, J.-i.; Nishimura, T. Discovery of novel 2-(pyridine-2-yl)-1H-benzimidazole derivatives as potent glucokinase activators. *Bioorg. Med. Chem. Lett.* **2009**, *19,* 4450. (e) Wolkenberg, S. E.; Zhao, Z.; Kapitskaya, M.; Webber, A. L.; Petrukhin, K.; Tang, Y. S.; Dean, D. C.; Hartmana, G. D.; Lindsley, C. W. Identification of potent agonists of photoreceptor-specific nuclear receptor (NR2E3) and preparation of a radioligand. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 5001. (f) Henary, M. M.; Wu, Y.; Fahrni, C. J. Zinc(II)-Selective Ratiometric Fluorescent Sensors Based on Inhibition of Excited-State Intramolecular Proton Transfer. *Chem. Eur. J.* **2004**, *10*, 3015. (g) Alfonso, M.; Tarraga, A.; Molina P. Ferrocenylbenzobisimidazoles for Recognition of Anions and Cations. *Inorg. Chem.* **2013**, *52,* 7487. (h) Kwok, W. H.; Zhang, H.; Payra, P.; Duan, M.; Hung, S.-c.; Johnston, D. H.; Gallucci, J.; Skrzypczak-Jankun, E.; Chan, M. K. Synthesis and Characterization of the Dimethyl-Substituted Bisbenzimidazole Ligand and Its Manganese Complex. *Inorg. Chem.* **2000,** *39,* 2367.

17. (a) Baars, H.; Beyer, A.; Kohlhepp, S. V.; Bolm, C. Transition-Metal-Free Synthesis of Benzimidazoles Mediated by KOH/DMSO. *Org. Lett.* **2014**, *16,* 536. (b) Sluiter, J.; Christoffers, J. Synthesis of 1-Methylbenzimidazoles from Carbonitriles. *Synlett* **2009**, *1*, 63. (c) Saha, P.; Ramana, T.; Purkait, N.; Ali, M. A.; Paul, R.; Punniyamurthy, T.

Ligand-Free Copper-Catalyzed Synthesis of Substituted Benzimidazoles, 2-Aminobenzimidazoles, 2-Aminobenzothiazoles, and Benzoxazoles. *J. Org. Chem.* **2009**, *74*, 8719.

18. (a) Mahesh, D.; Sadhu P.; Punniyamurthy, T. Copper(I)-Catalyzed Regioselective Amination of *N*-Aryl Imines Using $TMSN_3$ and TBHP: A Route to Substituted Benzimidazoles. *J. Org. Chem.* **2015,** *80,* 1644. (b) Blacker, A. J.; Farah, M. M.; Hall, M. I.; Marsden, S. P.; Saidi, O.; Williams, J. M. J. Synthesis of Benzimidazoles by Hydrozen-Transfer Catalysis. *Org. Lett.* **2009**, *11*, 9. (c) Ghosh, P.; Subba R. $MgCl_2.6H_2O$ catalyzed highly efficient synthesis of 2-substituted-1*H*-benzimidazoles. *Tetrahedron Lett.* **2015**, *56*, 2691.
19. (a) Dudd, L. M.; Venardou, E.; Garcia-Verdugo, E.; Licence, P.; Blake, A. J.; Wilson, C.; Poliakoff, M. Synthesis of benzimidazoles in high temperature water. *Green Chem.* **2003**, *5*, 187. b) Wright, J. B. The chemistry of the Benzimidazoles. *Chem. Rev.* **1951,** *48*, 397. c) Salikov, R. F.; Platonov, D. N.; Frumkin, A. E.; Lipilin, D. L.; Tomilov, Y. V. Synthesis of 2,3-dihydro-1*H*-pyrrolo[1,2-a]benzimidazoles *via* the cyclopropyliminium rearrangement of substituted 2-cyclopropylbenzimidazoles. *Tetrahedron,* **2013**, *69*, 3495. d) Charton, J.; Girault-Mizzi, S.; Debreu-Fontaine, M.-A.; Foufelle, F.; Hainault, I.; Bizot-Espiard, J.-G.; Caignard, D.-H.; Sergheraert, C. Synthesis and biological evaluation of benzimidazole derivatives as potent AMP-activated protein kinase activators. *Bioorg. Med. Chem.* **2006,** *14*, 4490. e) Wang J.; Wang, X.; Li, H.; Ji, D.; Li, Y.; Xu, Y.; Zhu, Q. Design, synthesis and biological evaluation of novel 5-fluoro-1*H*-benzimidazole-4-carboxamide derivatives as potent PARP-1 inhibitors. *Bioorg. Med. Chem. Lett.* **2016**, *26*, 4127. f) Lee, H. K.; Lee, Y. S.; Roh, E. J.; Rhim, H.; Lee, J. Y.;

Shin K. J. Synthesis and evaluation of α,α′disubstituted phenyl acetate derivatives for T-type calcium channel blockers. *Bioorg. Med. Chem. Lett.* **2008,** *18,* 4424. g) Rambabu, D.; Murthi, P. R. K.; Dulla, B.; Rao, M. V. B.; Pal, M. Amberlyst-15–Catalyzed Synthesis of 2-Substituted 1,3-Benzazoles in Water under Ultrasound. *Synth. Commun.* **2013**, *43*, 3083.

20. Nagao, I.; Ishizaka, T.; Kawanami, H. Rapid production of benzazole derivatives by a high-pressure and high-temperature water microflow chemical process. *Green Chem*., **2016**, *18*, 3494.
21. (a) Salehi, P.; Dabiri, M.; Zolfigol, M. A.; Otokesh, S.; Baghbanzadeh, M. Selective synthesis of 2-aryl-1-arylmethyl-1*H*-1,3-benzimidazoles in water at ambient temperature. *Tetrahedron Lett.* **2006,** *47,* 2557. (b) Chebolu, R.; Kommi, D. N.; Kumar, D.; Bollineni, N.; Chakraborti, A. K. Hydrogen-Bond-Driven Electrophilic Activation for Selectivity Control: Scope and Limitations of Fluorous Alcohol-Promoted Selective Formation of 1,2-Disubstituted Benzimidazoles and Mechanistic Insight for Rationale of Selectivity. *J. Org. Chem.* **2012**, *77*, 10158.
22. (a) Kim, Y.; Kumar, M. R.; Park, N.; Heo, Y.; Lee, S. Copper-catalyzed, one-pot, three-component synthesis of benzimidazoles by condensation and c–n bond formation. *J. Org. Chem.* **2011**, *76,* 9577. (b) Shen, M.; Driver, T. G. Iron (II) bromide-catalyzed synthesis of benzimidazoles from aryl azides. *Org. Lett.* **2008**, *10*, 3367. (c) Bahrami, K.; Khodaei, M. M.; Naali, F. Mild and highly efficient method for the synthesis of 2-arylbenzimidazoles and 2-arylbenzothizoles. *J. Org. Chem.* **2008**, *73*, 6835.
23. (a) Reddy, T. S.; Kulhari, H.; Reddy, V. G.; Bansal, V.; Kamal, A.; Shukla, R. Design, synthesis and biological evaluation of 1,3-diphenyl-1*H*-pyrazole derivatives containing

benzimidazole skeleton as potential anticancer and apoptosis inducing agents. *Eur. J. Med. Chem.* **2015,** *101,* 790. (b) Zheng, Y.; Zheng, M.; Ling, X.; Liu, Y.; Xue, Y.; An, L.; Gu, N.; Jin, M. Design, synthesis, quantum chemical studies and biological activity evaluation of pyrazole–benzimidazole derivatives as potent Aurora A/B kinase inhibitors. *Bioorg. Med. Chem. Lett.* **2013**, *23*, 3523.

24. (a) Prier, C. K.; Rankic, D. A.; MacMillan, D. W. C. Visible Light Photoredox Catalysis with Transition Metal Complexes: Applications in Organic Synthesis *Chem. Rev.* **2013**, *113*, 5322; (b) Ravelli, D.; Fagnoni, M. Dyes as Visible Light Photoredox Organocatalysts. *ChemCatChem* **2012**, *4*, 169.

25. Park, S.; Jung, J.; Cho, E. J. Visible-Light-Promoted Synthesis of Benzimidazoles. *Eur. J. Org. Chem.* **2014**, 4148.

26 Hu, J.; Wang, J.; Nguyen, T. H.; Zheng, N. The chemistry of amine radical cations produced by visible light photoredox catalysis. *Beilstein J. Org. Chem.* **2013**, *9*, 1977.

27 (a) Condie, A. G.; Gonzalez-Gomez, J. C.; Stephenson, C. R. J. Visible-Light Photoredox Catalysis: Aza-Henry Reactions via C-H Functionalization. *J. Am. Chem. Soc.* **2010,** *132,* 1464. (b) Hoffmann, N. Efficient photochemical electron transfer sensitization of homogeneous organic reactions. *J. Photochem. Photobiol. C,* **2008,** *9,* 43. (c) Niu, T.-f.; Li, L.; Ni, B.-q.; Bu, M.-j.; Cai, C.; Jiang, H.-l. Visible-Light-Induced Meerwein Cascade Reactions for the Preparation of α-Aryl Esters. *Eur. J. Org. Chem.* **2015,** 5775.

Table of Contents Graphic: