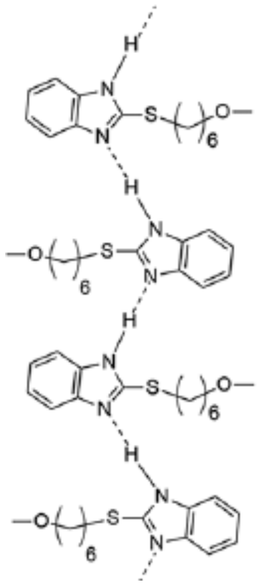
Garden of Knowledge and Virtue
LEADING THE WAY
KHALĪFAH • AMĀNAH • IQRA' • RAḤMATAN LIL-ĀLAMĪN
Greater Gombak
REGIONAL CENTRE OF EXPERTISE ON EDUCATION FOR SUSTAINABLE DEVELOPMENT
ACKNOWLEDGED BY
UNITED NATIONS UNIVERSITY
AN INTERNATIONAL AWARD-WINNING INSTITUTION FOR SUSTAINABILITY
UTHM
Universiti Tun Hussein Onn Malaysia
Virtual
SCIEMATHIC2021
"The Quest for Sustainable Science and Mathematics Research for Future Technologies"
OCTOBER 27th-28th 2021

Benzimidazole as a Versatile Scaffold for Biologically Active Molecules: Structure and drug design targeting the epidermal growth factor receptor (EGFR)

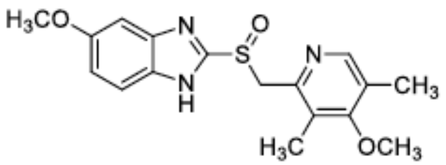
Shafida Abd Hamid

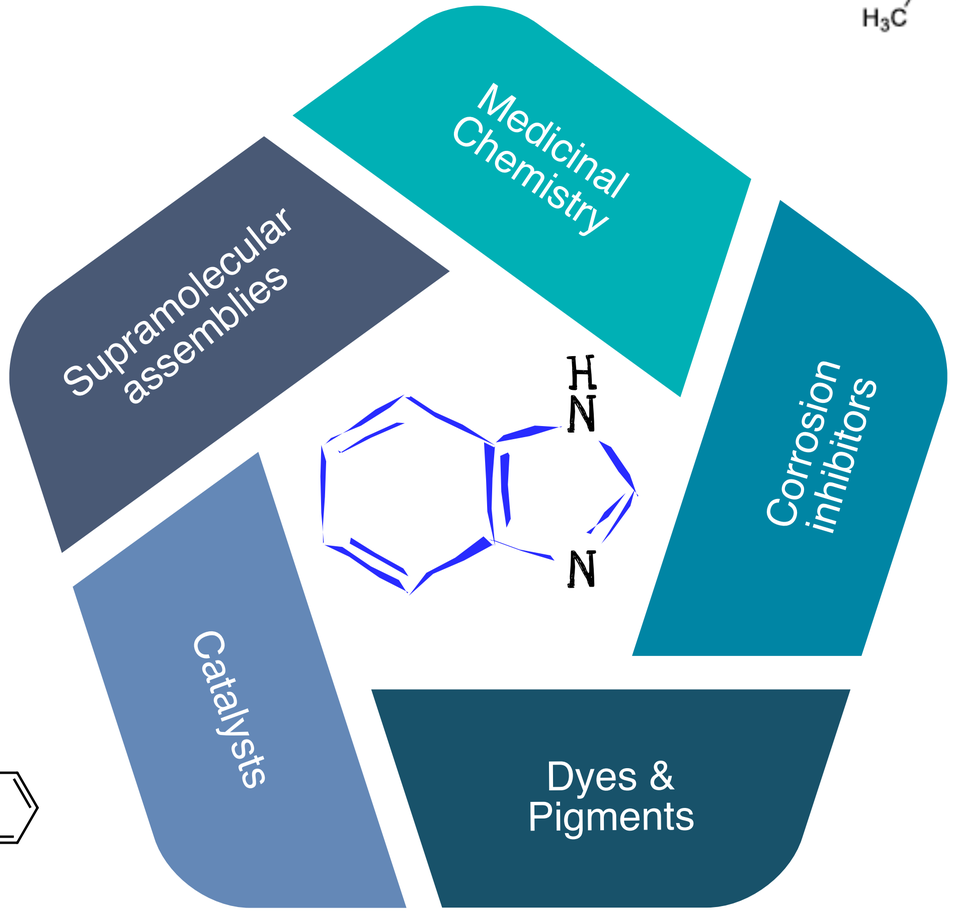
IIUM KUANTAN
DEPARTMENT OF CHEMISTRY
KULLIYYAH OF SCIENCE

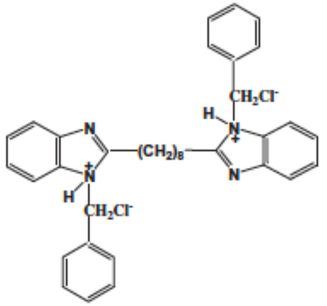
Applications of Benzimidazoles



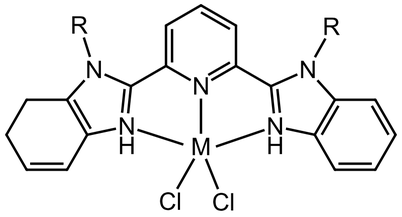
Tan et al., RSC Adv., 2016, 6, 34038



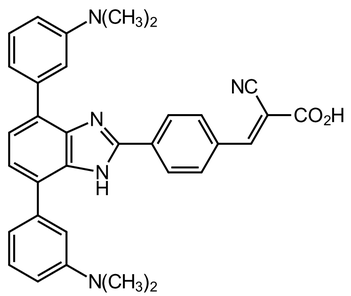




Wang et al., Corrosion Science,2011,53, 113-121

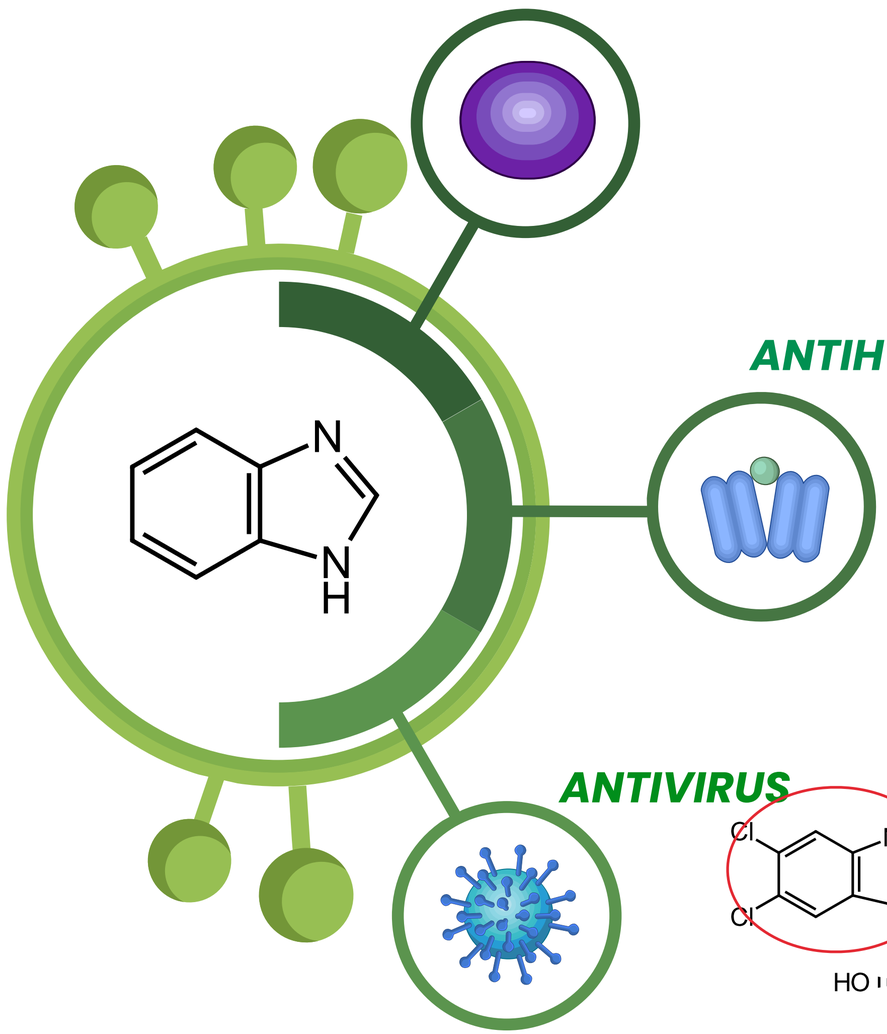


Kirpik et al., App. Organomet. Chem, 2020

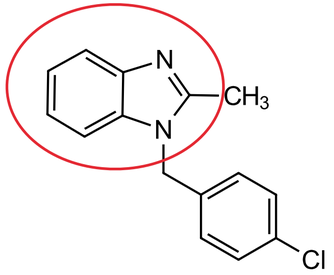


Saltan et al., Mat. Chem. Phys.,2015,163, 387-393

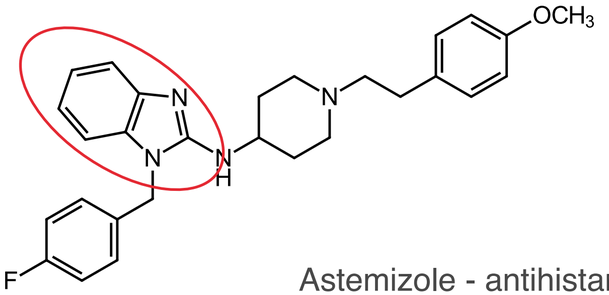
Benzimidazole : A Privileged Scaffold in Drug Discovery



ANTIBACTERIAL

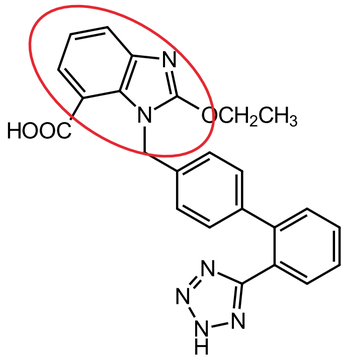


Chlormidazole - antifungal

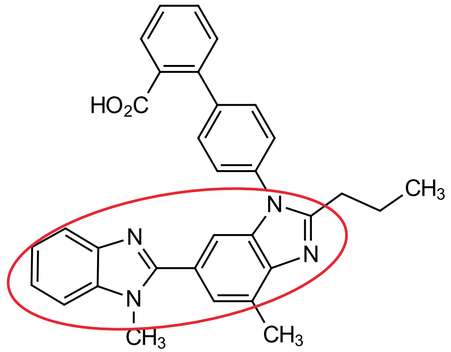


Astemizole - antihistamine

ANTIHYPERTENSIVE

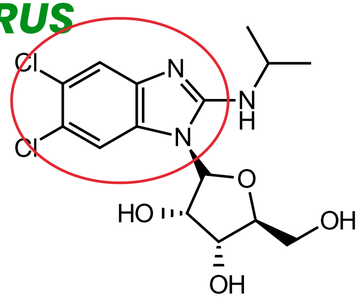


Candesartan

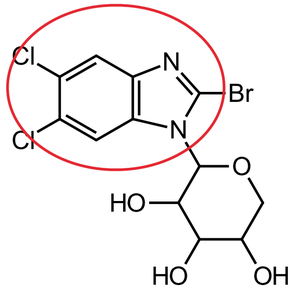


Telmisartan

ANTIVIRUS

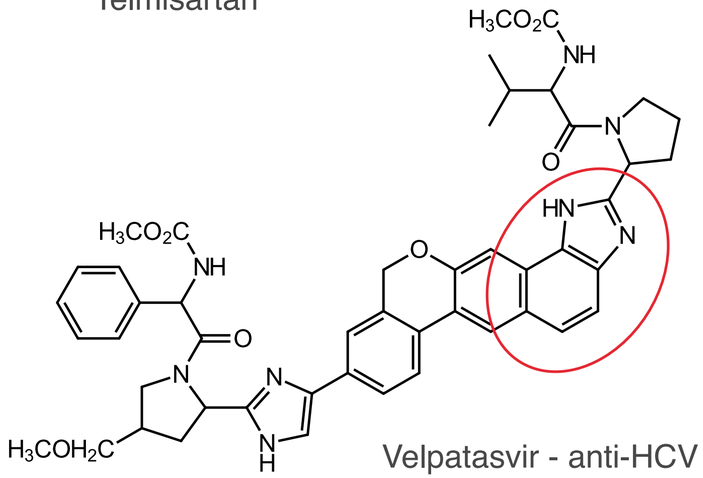


Maribavir

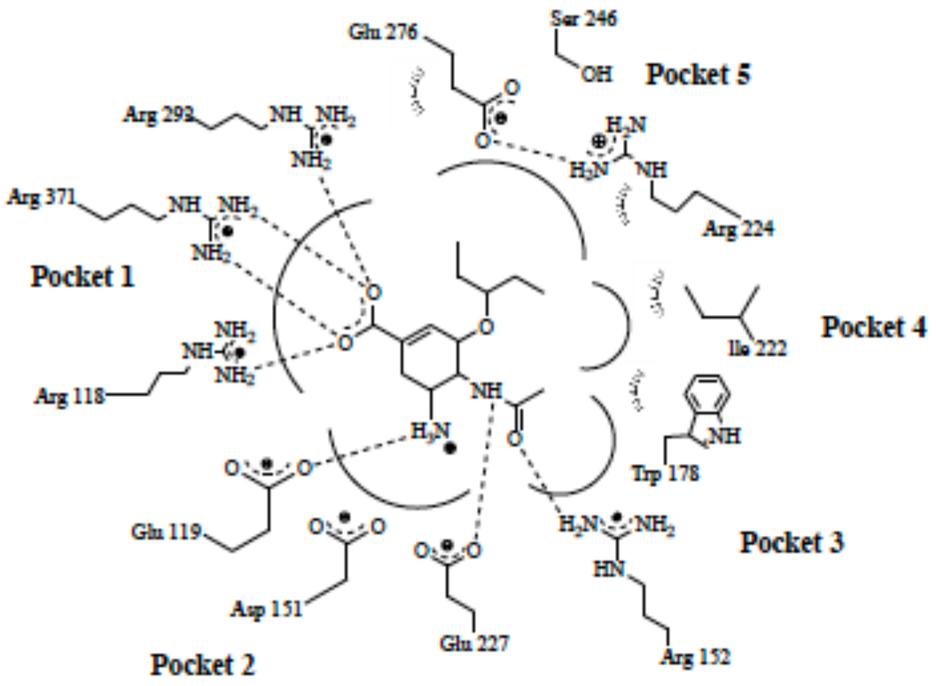


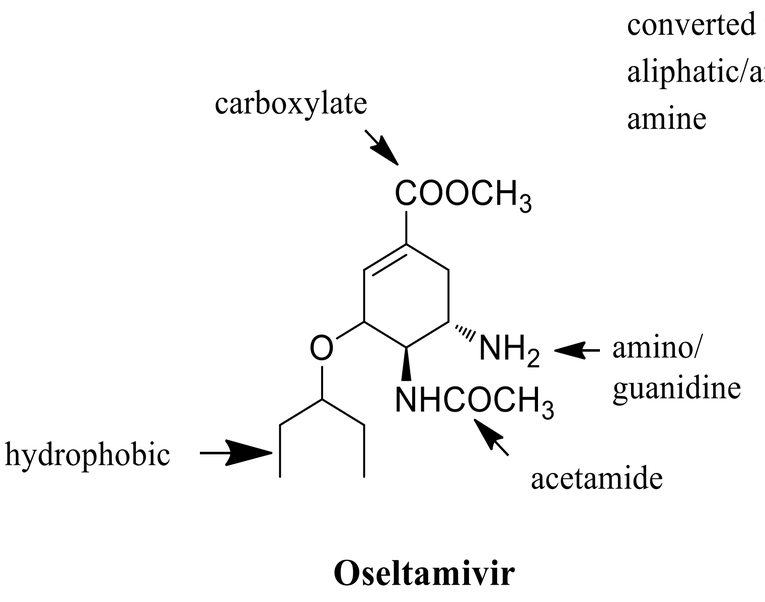
GW 275175X

anti-CMV

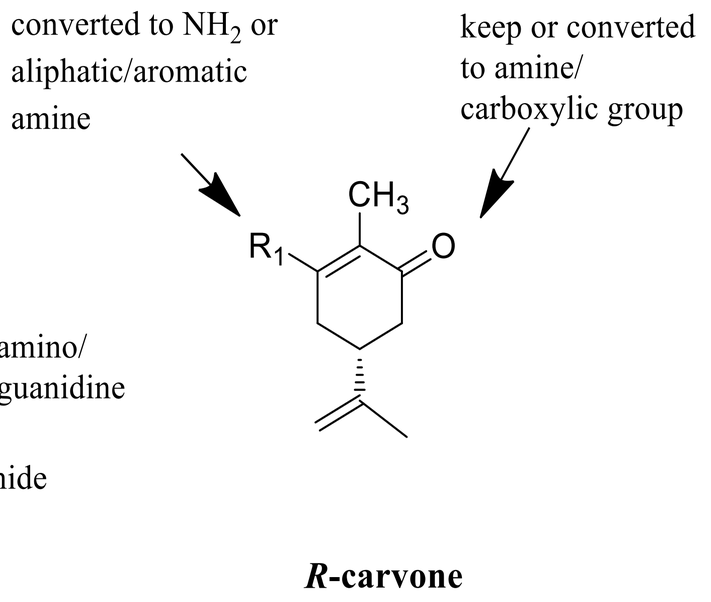


Velpatasvir - anti-HCV



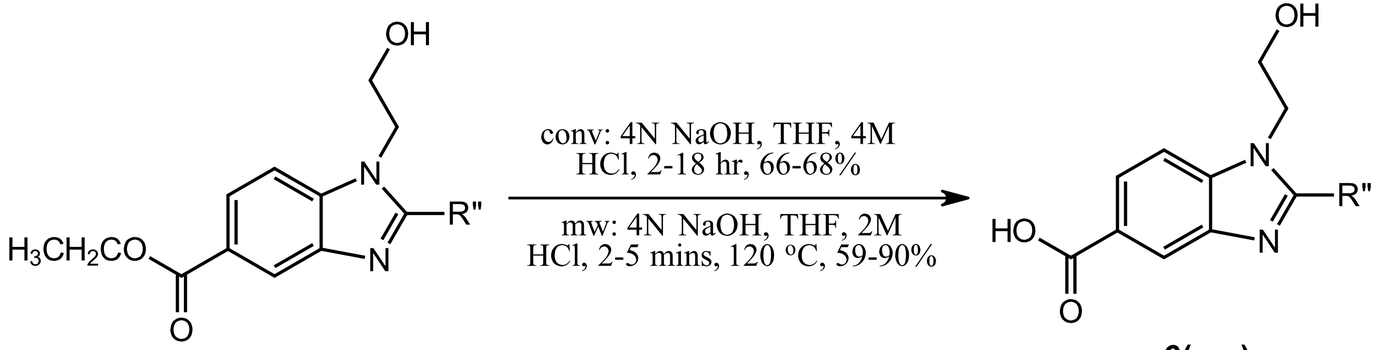


Oseltamivir



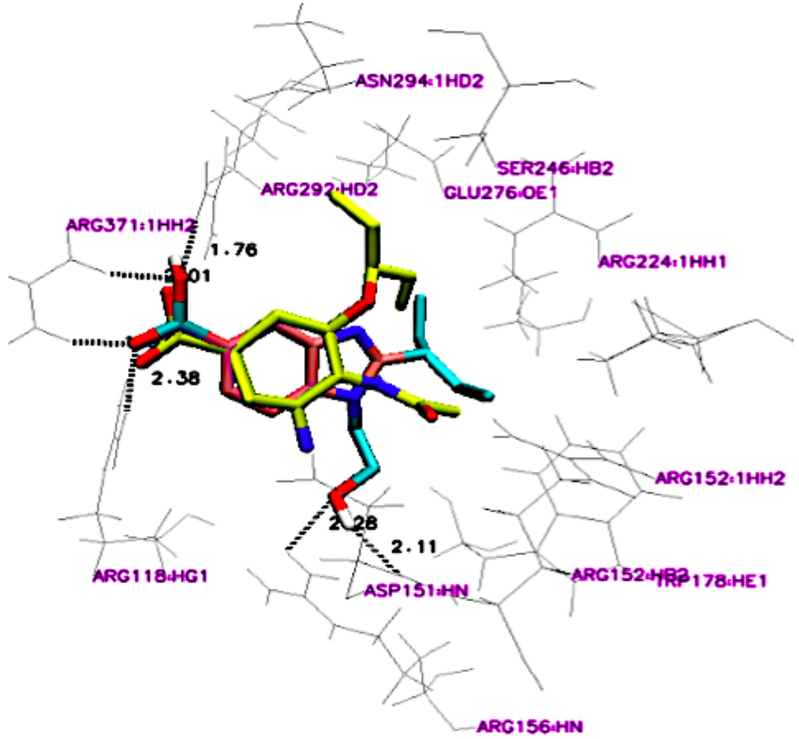
***R*-carvone**

Von Itzstein & Thomson, 2009

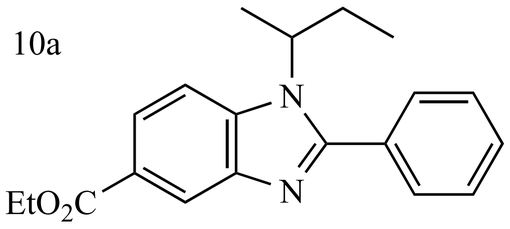


5(a-g) **6(a-g)**

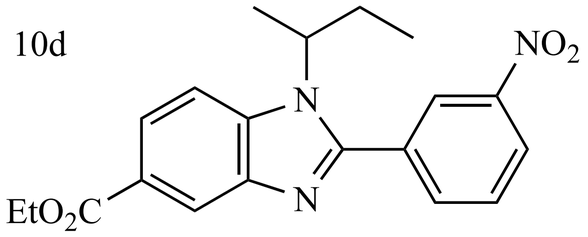
R" = **6a :** $-CH_2CH_3$
6b : $-CH(CH_3)_2$
6c : $-CH_2CH_2CH_3$
6d : $-CH_2(CH)_2CH_3$
6e : $-CH_2(CH_3)CH_CCH_3$
6f : $-CH(CH_2CH_3)_2$
6g : $-CH_2SCH_2CH_3$



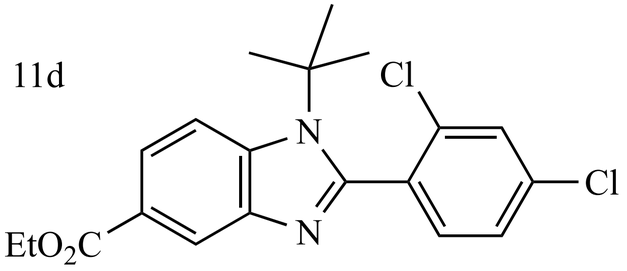
10a



10d

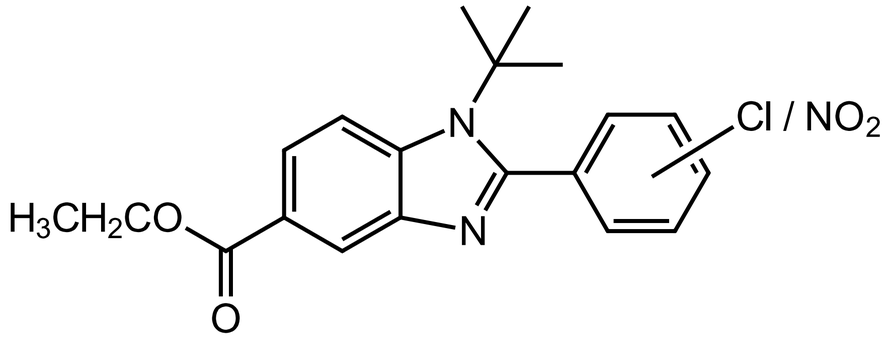


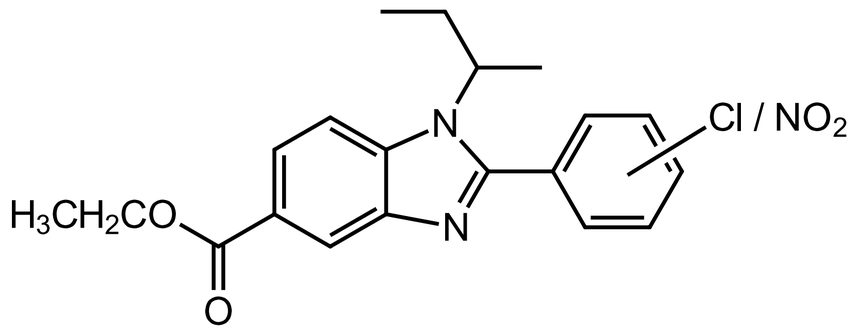
11d



	IC_{50} (μM)	
	MDA-MB-231	MCF-7
10a	29.7	>200
10d	36.8	>200
11d	47.6	>200

Abd Rahim et al., 2012





RECEPTORS

cellular signalling activities, including cells' growth, proliferation, differentiation, metabolism, migration and apoptosis

EGFR MUTATION

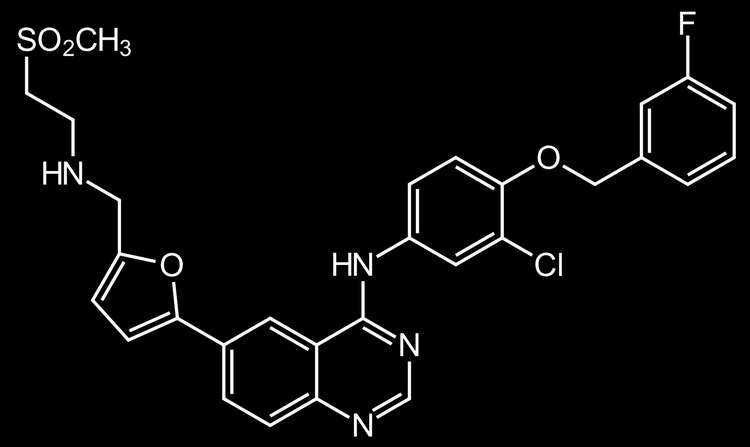
overexpression of genes and uncontrolled cell growth in various human tumours

EGFR-TARGET THERAPY

Tyrosine kinase inhibitors (TKIs) would compete with the ligands to reduce the expression

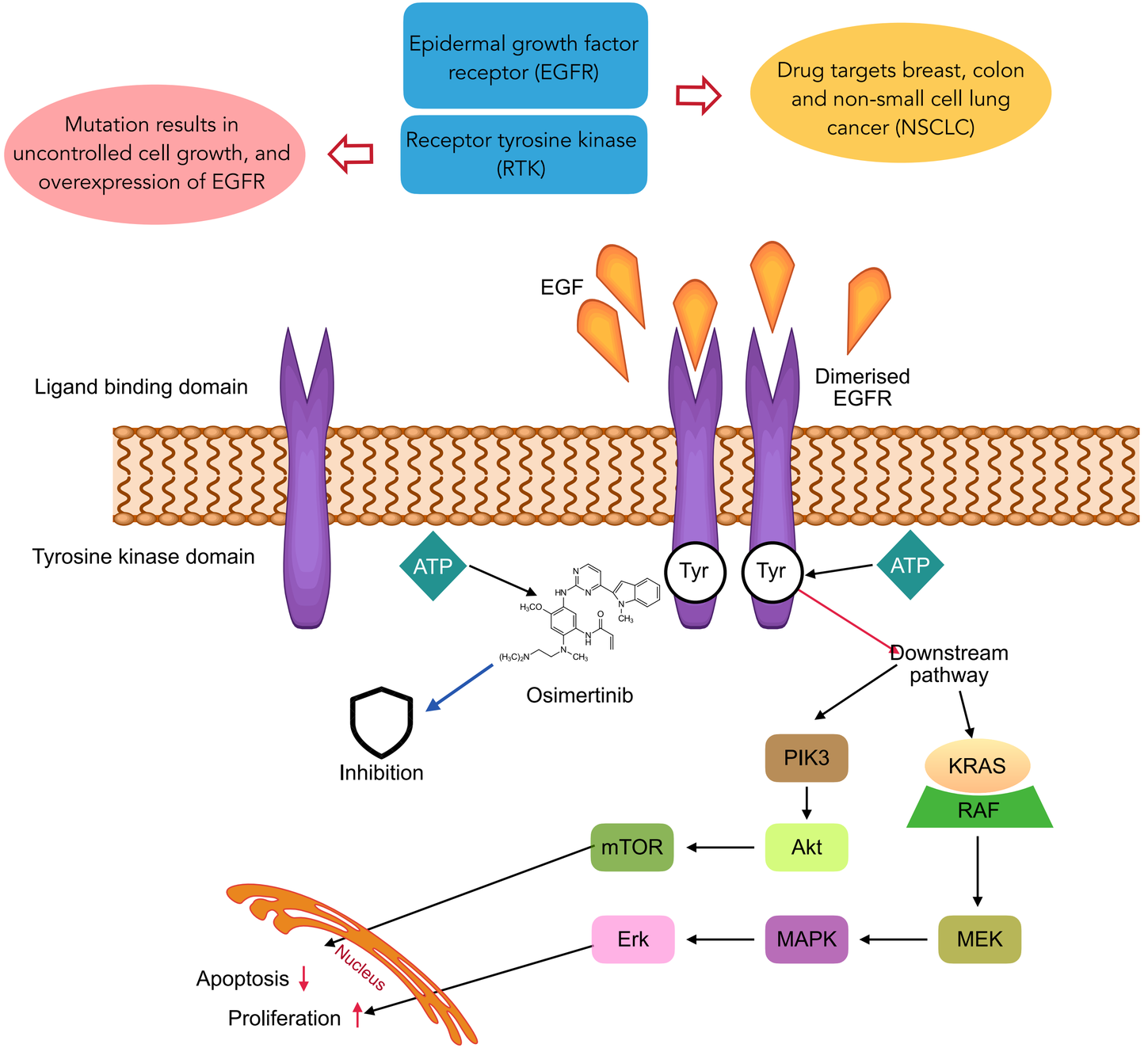
KINASE INHIBITORS

drugs targeting various cancer-related protein kinases have been developed



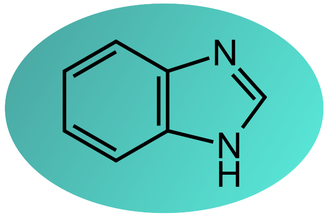
Lapatinib

Erlotinib

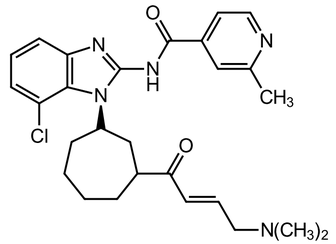


Adapted from Araki et al., 2012, 6, 407-421

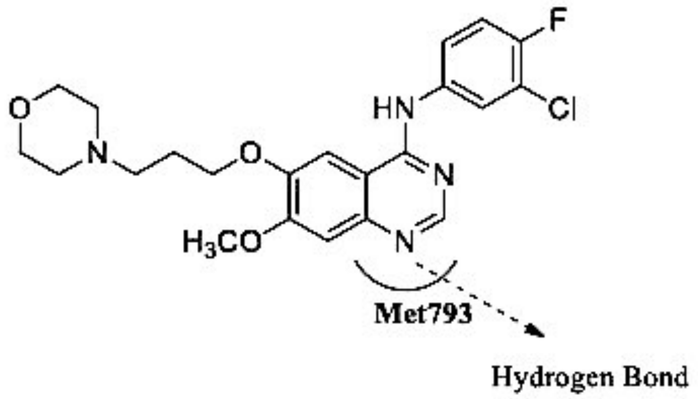
Design of typrosine kinase inhibitors (TKIs)



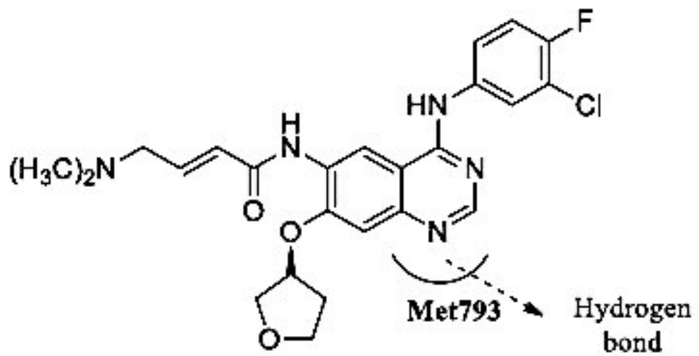
Potential benzimidazole-based TKIs



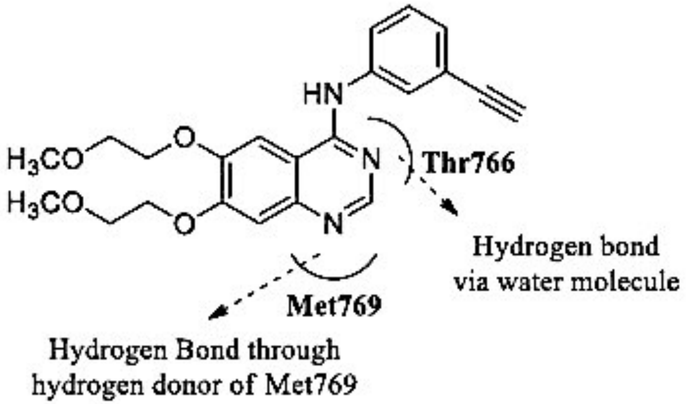
Fourth generation of TKIs?



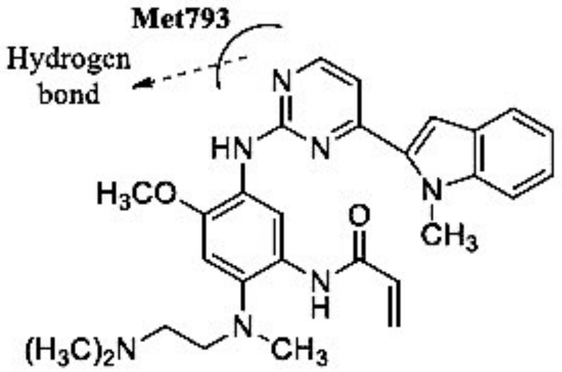
Gefitinib



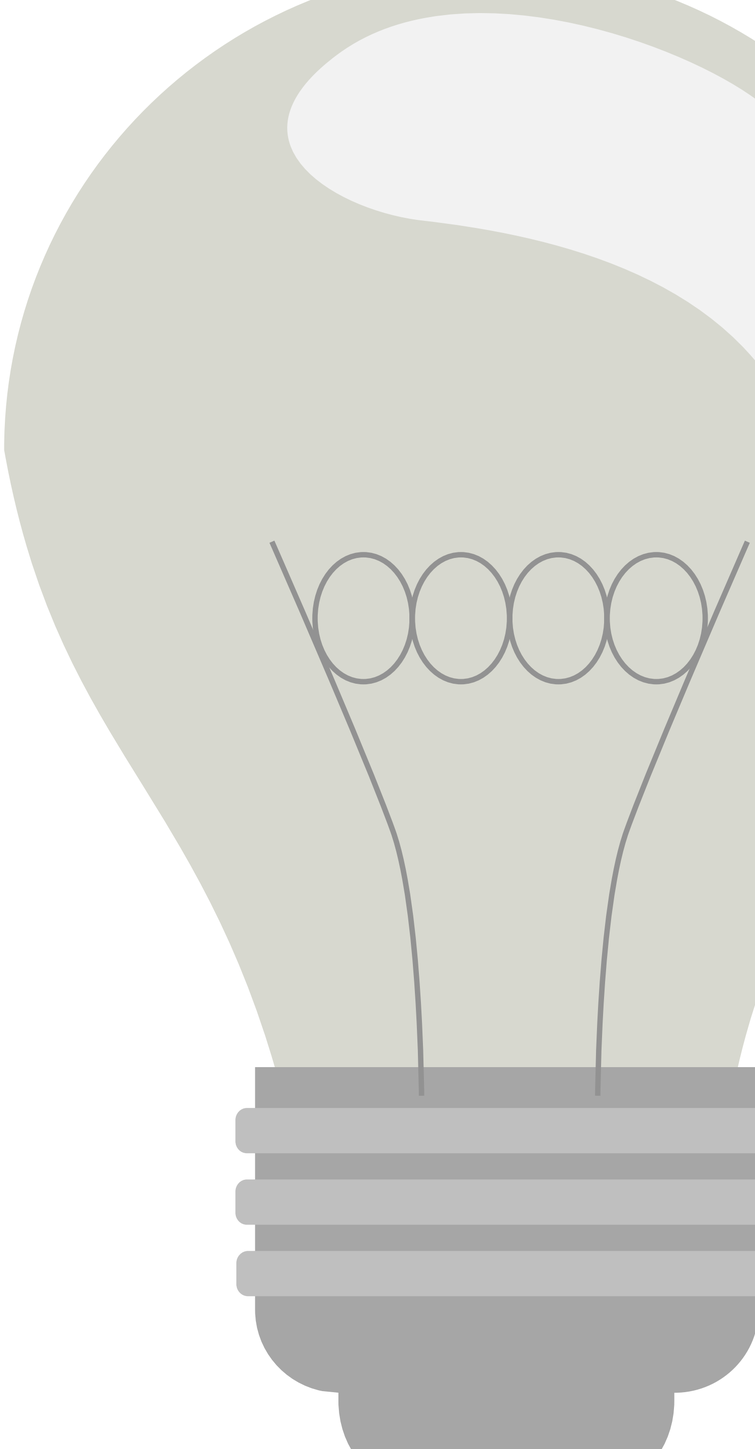
Afatinib

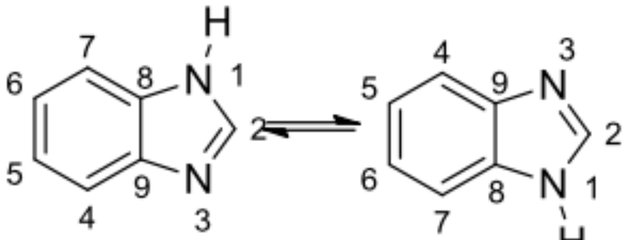


Erlotinib

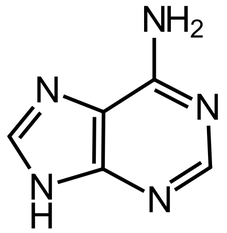


Osimertinib

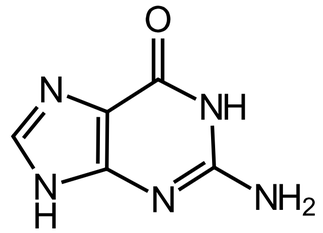




Lead compound



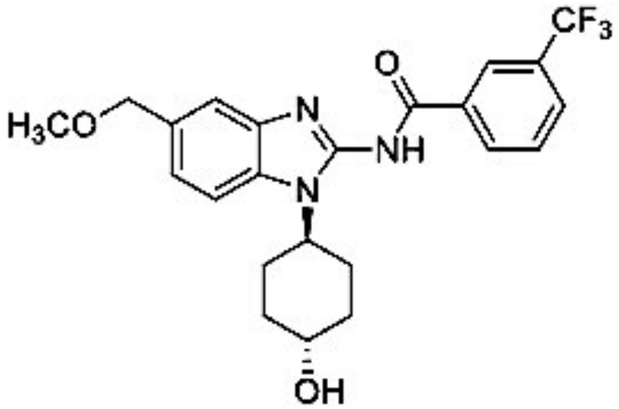
adenine



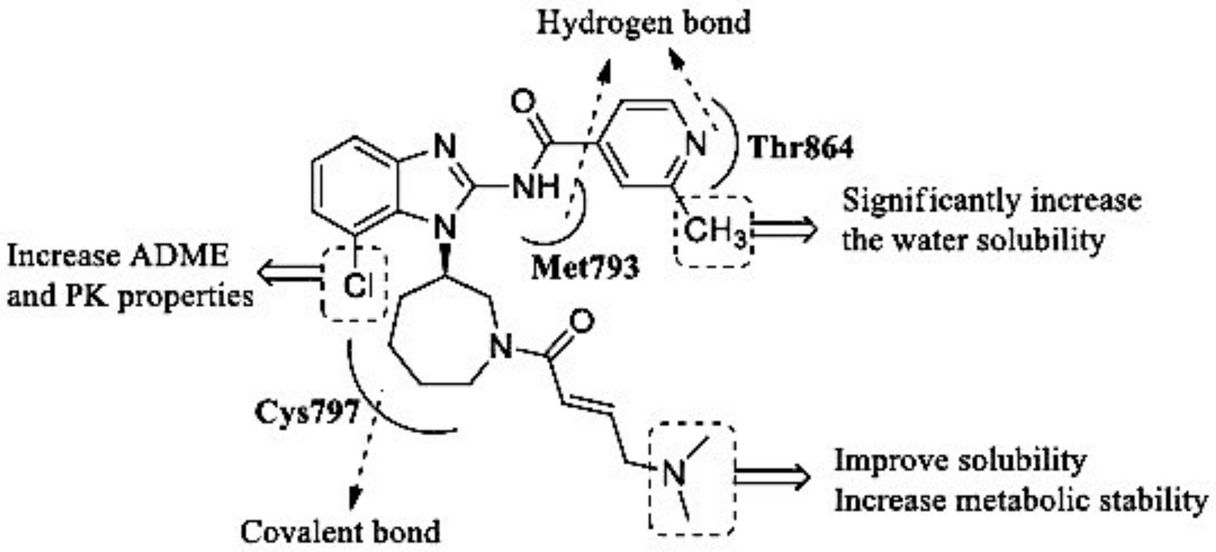
guanine

Building block of DNA and RNA

SAR of Benzimidazoles and EGFR-Expressing Cancer Cell Lines

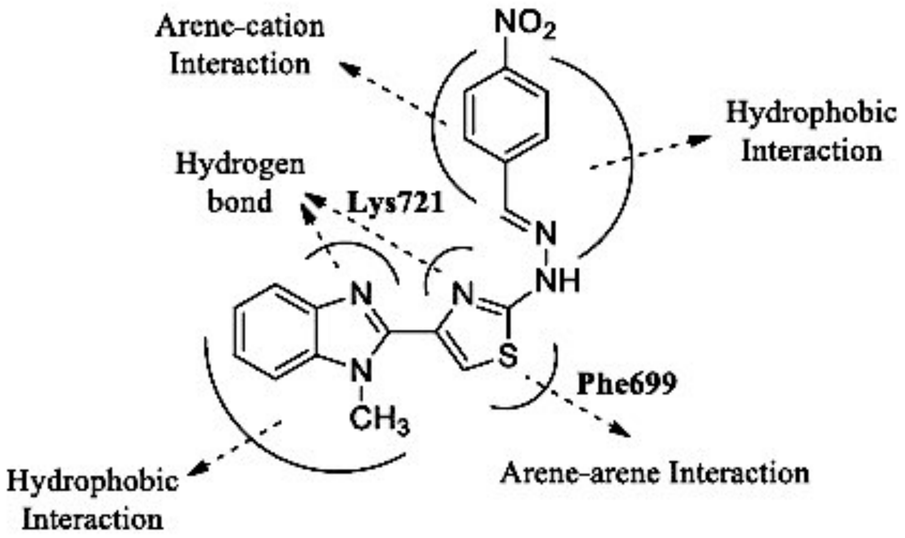


A



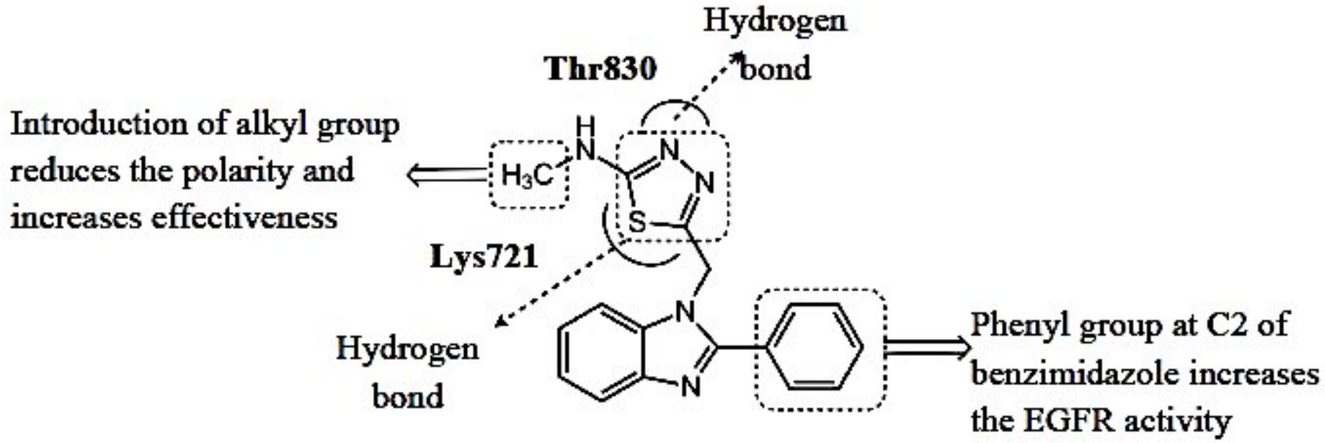
Lelais et al. (2016)

Thiazole ring bonded to the benzimidazole



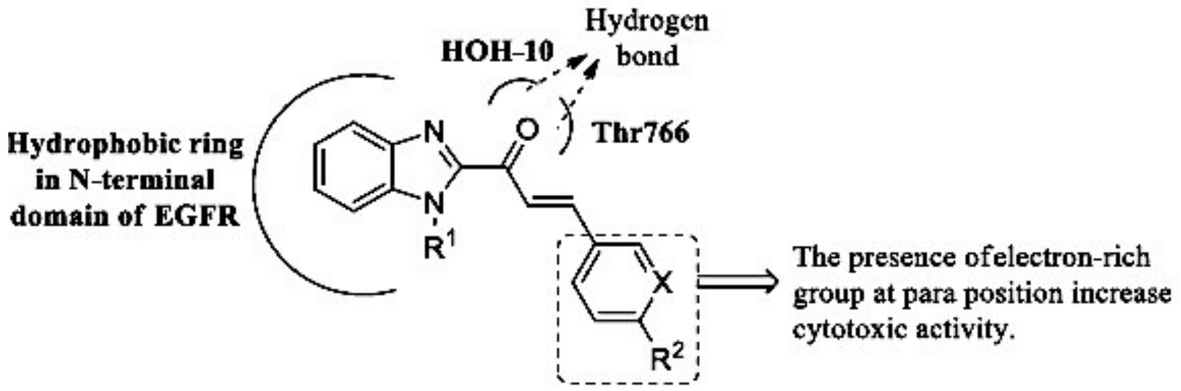
Srour et al. (2020)

Thiadiazole ring bonded to the benzimidazole



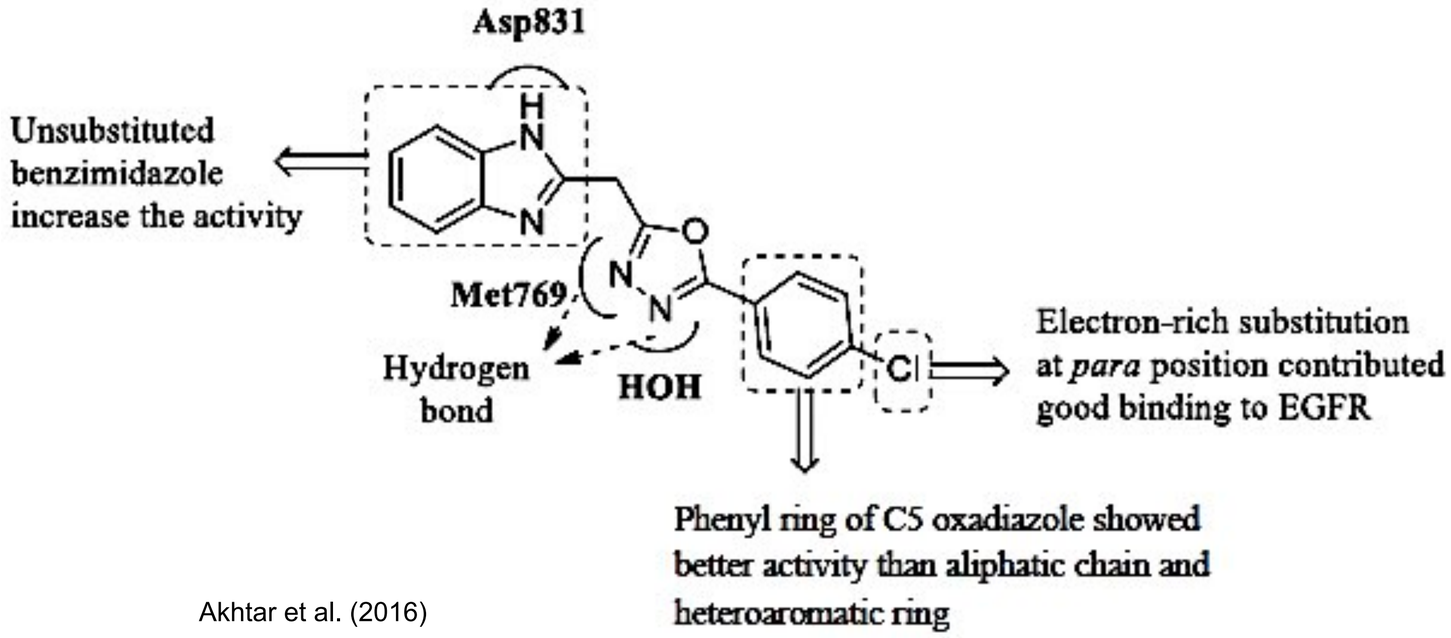
Celik et al. (2019)

Substituted benzimidazolechalcones and pyrazinobenzimidazole derivatives



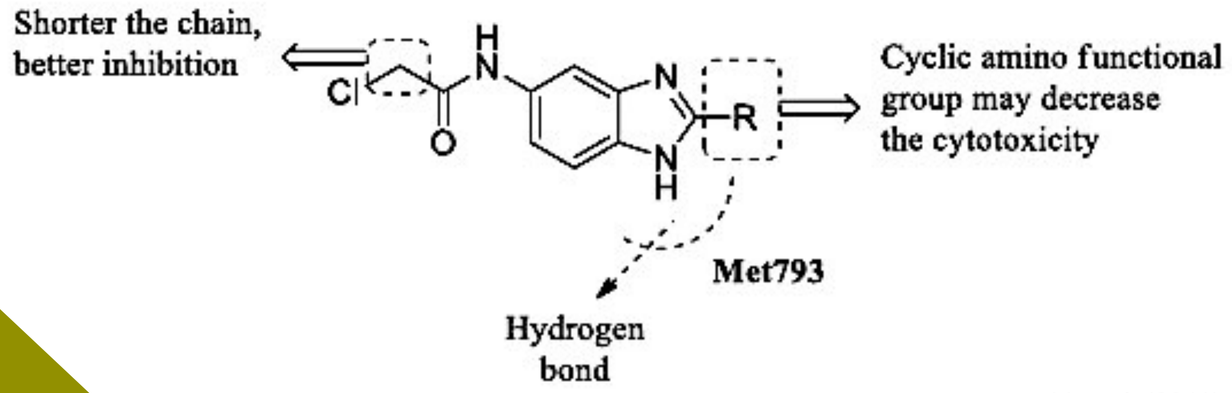
Mohamed et al. (2017)

Oxadiazole-linked benzimidazoles

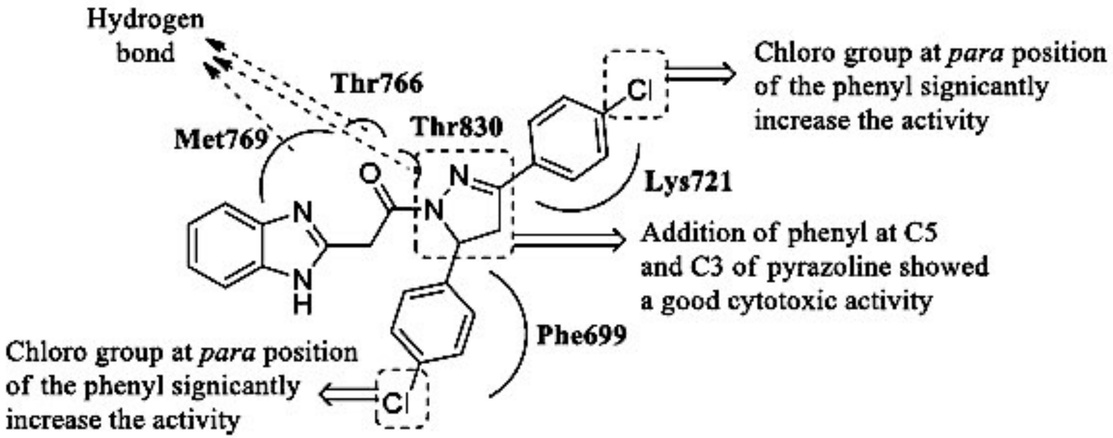


Akhtar et al. (2016)

Pyrazoline-benzimidazole derivatives

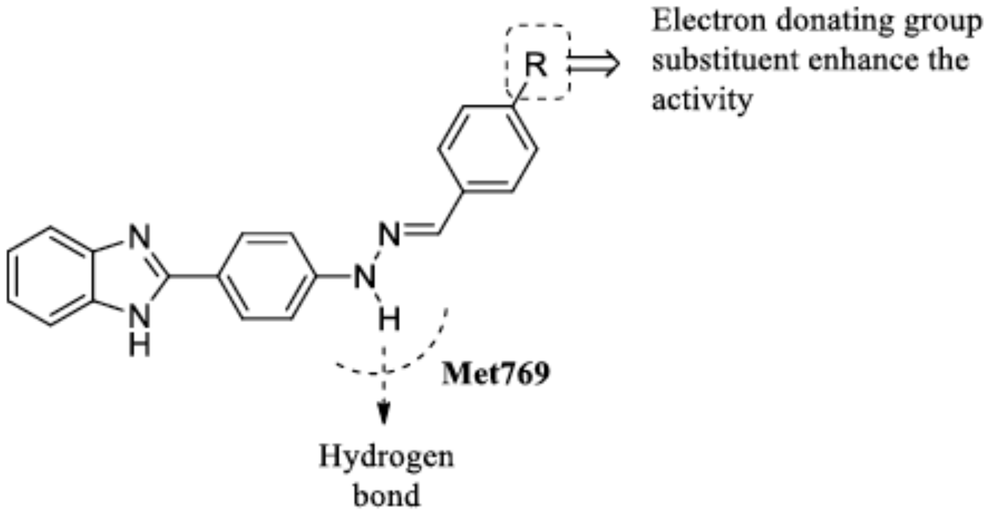


Li et al. (2011)



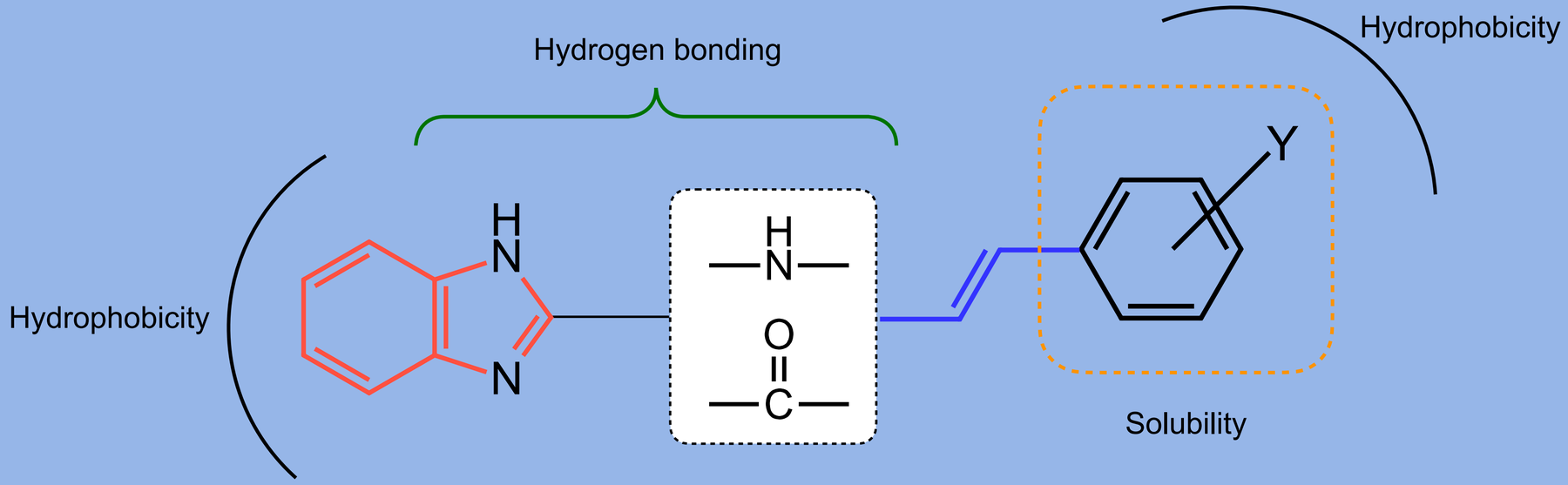
(Akhtar et al., 2018)

Hydrazinyl-benzimidazole derivatives



(Labib et al., 2018)

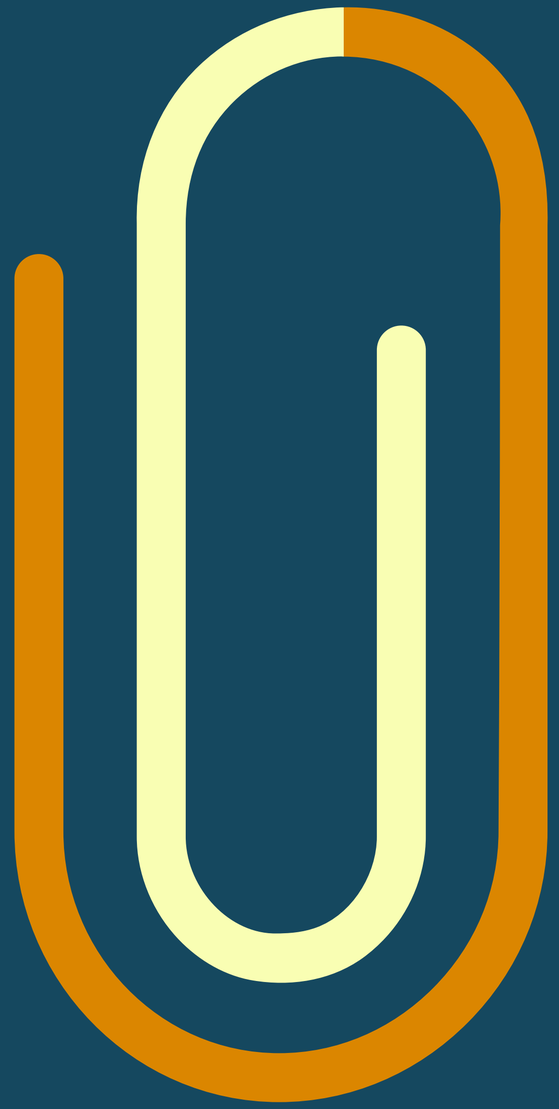
SUMMARY



Abdullah et al., 2021

CONCLUSION

- Despite the EGFR mutations, the structure and biological activity evaluation of the currently used drugs are still taken as the principal approach in the development of inhibitors in facing the challenges in cancer treatment.
- In most cases, studies imply that interaction at Met793 is significant in EGFR activity, as shown in gefitinib, afatinib, osimertinib and nazartinib
- Many of the reported compounds showed inhibition to EGFR by binding mainly to Met793, others showed association with Met769 and Thr766, similar to erlotinib
- Advanced computational simulations (apart from molecular docking) could be used to gather more information on the properties of the synthesised compounds more precisely so that more effective compounds can be designed (or re-designed) for potential tyrosine kinase inhibitors



ACKNOWLEDGMENTS

Mar'iyah Najihah Abdullah

Yousaf Ali

Noor Akmar Jusoh

Ministry of Higher Education

Kulliyyah of Science, IIUM

THANKS

International Conference on the Application of Science and Mathematics

27th – 28th October 2021

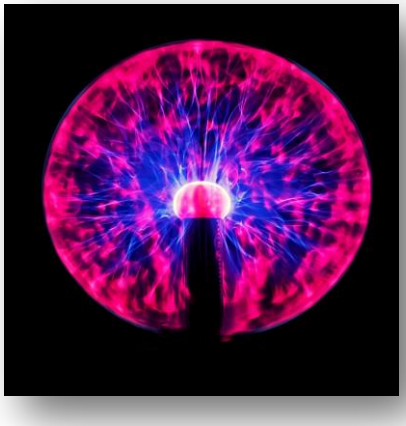
"The Quest for Sustainable Science and Mathemathics Research for Future Technologies"

SCIEMATHIC2021

Organized by:

UTHM
Universiti Tun Hussein Onn Malaysia

FAST
Fakulti Sains Gunaan dan Teknologi
Universiti Tun Hussein Onn Malaysia



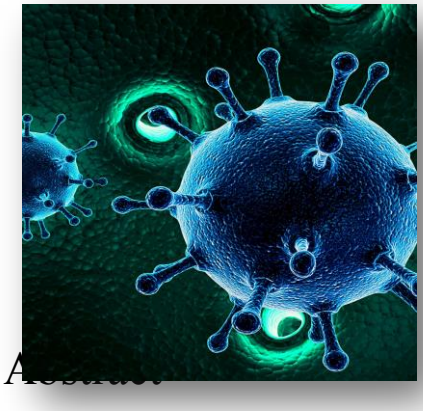


TABLE OF CONTENTS

TENTATIVE OF PROGRAMME

27 October 2021 (Wednesday)

08.00 - 08.30am	Arrival of participants and guests
08.30 - 08.45am	FAST Corporate video
08.45 - 08.50am	Doa
08.50 - 09.00am	Welcoming Speech **Ts. ChM. Dr. Zalilah Murni Yunus** Conference Chair of SCIEMATHIC 2021
09.00-09.45am	Keynote Speaker 1: **Assist. Prof. Dr. Satoru Yoshioka** Quantum Sciences of Materials, Department of Applied Quantum Physics and Nuclear Engineering, Faculty of Engineering, Kyushu University
09.45 - 1.00pm	**Parallel Sessions**
1.00 - 2.00pm	BREAK
2.00 - 3.00pm	Keynote Speaker 2 : **Assoc. Prof. Dr. John Richard Pasley** York Plasma Institute, Department of Physics, University of York, United Kingdom
3.00 - 3.45pm	Keynote Speaker 3 : **Dr. Muhammad Shahbaz Anwar** Department of Materials Science and Metallurgy University of Cambridge, United Kingdom
3.45-4.15pm	Invited Speaker 1: **Dr. Saiful Najmee bin Mohammad** Faculty of Applied Sciences, Universiti Teknologi MARA
4.15 - 4.45pm	Invited Speaker 2: **Prof. Dr. Shafida Abd Hamid** Department of Chemistry Kulliyyah of Science, International Islamic University Malaysia
4.45 - 5.15pm	Invited Speaker 3: **Mr. Abd Rahim bin Othman** Process Department Group Technical Solution, Technology & Engineering Division,Petroliam Nasional Berhad

TENTATIVE OF PROGRAMME

28 October 2021 (Thursday)

08.30 - 08.40am	Conference Remark **Dr. Fahmiruddin Esa** Head of Department Physics and Chemistry
08.40 - 11.15pm	**Parallel Sessions**
OPENING AND CLOSING CEREMONY	
11.30 - 11.35pm	Speech 1**:** **Prof. Dr. Hashim bin Saim** Dean Faculty of Applied Sciences and Technology
11.35 - 11.55pm	Inauguration Speech **Dato' Sri Ibrahim Ahmad** Chairman UTHM Board of Directors
11.55- 11.57pm	Montage impression of SCIEMATHIC 2021
MOU SIGNING CEREMONY	
11.57 - 12.00pm	MOU Signing
12.00 - 12.15pm	Video Presentation
12.15 - 12.40pm	Speech 2: **Dato' Dr. Mohamad Zabawi bin Abdul Ghani** Director General of MARDI Speech 3: **Prof. Dr. Muhammad Ashraf** Rector University of Lahore Speech 4: **Mr. Zaliman Zali** Head of Sales, UWG Marketing & Distributors Sdn. Bhd
12.40 - 12.50pm	Speech 5 : **Prof. Datuk Ts. Dr. Wahid bin Razzaly** Vice Chancellor UTHM Universiti Tun Hussein Onn Malaysia
BREAK	
2.00 - 2.45pm	Keynote Speaker 4 : **ChM. Dr. Fatimah Salim** Research Fellow, Atta-ur-Rahman Institute for Natural Product Discovery, Universiti Teknologi MARA
END	

Benzimidazole as a Versatile Scaffold for Biologically Active Molecules: Structure and drug design targeting the epidermal growth factor receptor (EGFR)

Shafida Abd Hamid

Department of Chemistry Kulliyyah of Science, International Islamic University Malaysia

Abstract: Benzimidazole is regarded as one of the privileged structures, which can be manipulated for designing various biologically active molecules. The heterocyclic compound is extensively investigated for inhibitory activity against enzymes or receptors such as epidermal growth factor receptor (EGFR) through modification of functional groups. Various marketed drugs with benzimidazole scaffolds to fight many diseases show the importance of this pharmacophore in medicinal chemistry. Interest in benzimidazole derivatives as anticancer agents is attributed to their stability, bioavailability and their ability to target the receptors. However, the challenge in targeted cancer therapy remains in addressing the issues involving toxicity, non-selectivity and resistance due to mutations. The development of the three generations of tyrosine kinase inhibitors (TKIs) based on the reported structure-activity relationship (SAR) of the drugs is essential to generate ideas in designing more potent inhibitors. In view of the SAR of the current anticancer drugs, and the extensive range of therapeutic applications of benzimidazole derivatives, could benzimidazoles be considered in the design of the next generation of TKIs?