Comment on "Modelling physico-chemical properties of (benzo)triazoles, and screening for environmental partitioning [Bhhatarai and Gramatica, Water Res. 45, 2011, 1463-1471]"

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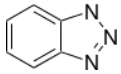
In their article, Bhhatarai and Gramatica [1] employ a quantitative structure-property relationship (QSPR) approach to model the physico-chemical properties of compounds they refer to as benzotriazoles, and to subsequently screen these compounds for environmental partitioning behavior. In their Supplementary Materials, the authors include a table entitled "SI4: The experimental and Predicted [sic] values (in Bold [sic]) for 66 (benzo)triazoles within the structural AD of all the models and with at least one experimental value for WS, logK and VP." Benzotriazoles have the following general structure:



Thus, of the 66 compounds that Bhhatarai and Gramatica [1] claim are benzotriazoles in Table SI4, it appears that only 7 compounds actually are benzotriazoles. The following 59 out of 66 training set compounds used to develop the QSPR model in Bhhatarai and Gramatica [1] appear to be erroneously classified (CAS numbers provided by Bhhatarai and Gramatica [1] were converted to structures and names [where available] using SPARC [http://archemcalc.com/sparc/; October 2011 release w4.6-.1691-s4.6.1687]):

- **1**. CAS 86500: azinphos methyl
- **3**. CAS 134587: 5-amino-1,4-dihydro-7H-1,2,3-triazolo[4,5-d]pyrimidin-7-one
- **5**. CAS 273405: 1H-1,2,3-triazolo[4,5-d]pyrimidine
- **6**. CAS 1031476: P-(5-amino-3-phenyl-1H-1,2,4-triazol-1-yl)-N,N,N',N'-tetramethyl-(8CI9CI)-phosphonic diamide
- **7**. CAS 1455772: 3,5-diamino-1,2,4-triazole
- **10**. CAS 2642719: azinphos ethyl
- **11**. CAS 2683901: 8-azahypoxanthine
- **12**. CAS 3357424: 3-phenyl-1H-1,2,4-triazole
- **13**. CAS 4368687: 1-benzyl-1,2,3-triazole
- **14**. CAS 6085945: 1-(phenylmethyl)-1H-1,2,4-triazole
- **16**. CAS 14500233: 4-methyl-1-phenyl-1,2,4-triazolidine-3,5-dione
- **18**. CAS 24017478: phosphorothioic acid, O,O-diethyl, O-(1-phenyl-1H-1,2,4-triazol-3-yl)ester
- **19**. CAS 26621454: 1-methyl-3-nitro-1,2,4-triazole
- **20**. CAS 28911015: triazolam
- **21**. CAS 28981977: alprazolam
- **22**. CAS 36791045: 1-β-D-ribofuranosyl-1H-1,2,4-triazole-3-carboxamide
- **23**. CAS 41083118: azocyclotin
- **24**. CAS 41814782: tricyclazole
- **25**. CAS 42509808: isazophos
- **26**. CAS 43121433: amiral
- **27**. CAS 55179312: bitertanol
- **28**. CAS 55219653: β-(4-chlorophenoxy)-α-(1,1-dimethylethyl)-1H-1,2,4-triazole-1-ethanol
- **29**. CAS 57801817: 2-bromo-4-(2-chlorophenyl)-9-methyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepine
- **31**. CAS 60207310: unnamed
- **32**. CAS 60207901: propiconazole
- **33**. CAS 60207934: etaconazole

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– **34**. CAS 66246886: 1-[2-(2,4-dichlorophenyl)pentyl]-1H-1,2,4-triazole

– **35**. CAS 66535862: 2-(4-chlorophenyl)-(1,2,4)triazolo[5,1-a]isoquinoline

– **36**. CAS 68049832: 2-[2,4-dichloro-5-(2-propynyloxy)phenyl]-5,6,7,8-tetrahydro-1,2,4-triazolo-[4,3-a] -pyridin-3(2H)-one

– **37**. CAS 69141500: (5R,6R)-rel-6-hydroxy-2,2,7,7-tetramethyl-5-(1H-1,2,4-triazol-1-yl)-3-octanone

– **38**. CAS 75736333: (α-R,-R)-rel-β-[(2,4-dichlorophenyl)methyl]-α-(1,1-dimethylethyl)-1H-1,2,4-triazole-1-ethanol

– **39**. CAS 76674210: flutriafol

– **40**. CAS 77314773: 4-(5-amino-1H-1,2,4-triazol-3-yl)-N-ethyl-2-pyridinamine

– **41**. CAS 79983714: α-butyl-α-(2,4-dichlorophenyl)-1H-1,2,4-triazole-1-ethanol

– **42**. CAS 82200724: triadimenol

– **43**. CAS 83657174: uniconazole

– **44**. CAS 83657221: [(4-chlorophenyl)methylene]-α-1H-1,2,4-triazole-1-ethanol

– **45**. CAS 83657243: diniconazole

– **46**. CAS 86598927: imibenconazole

– **47**. CAS 88671890: myclobutanil

– **48**. CAS 89482177: triadimenol

– **49**. CAS 94361065: cyproconazole

– **50**. CAS 98967409: flumetsulam

– **51**. CAS 104958852: N-(2-hydroxy)ethyl-(3-nitro-1,2,4-triazol-1-yl)acetamide

– **52**. CAS 107534963: tebuconazole

– **53**. CAS 112281773: tetraconazole

– **54**. CAS 114369436: fenbuconazole

– **55**. CAS 116255482: bromuconazole

– **56**. CAS 119126157: flupoxam

– **57**. CAS 119446683: difenoconazole

– **58**. CAS 122836355: sulfentrazone

– **59**. CAS 125116236: metconazole

– **60**. CAS 125225287: ipconazole

– **61**. CAS 125306834: CH-900

– **62**. CAS 128639021: α-2-dichloro-5-[4-(difluoromethyl)-4,5-dihydro-3-methyl-5-oxo-1H-1,2,4-triazol-1-yl]-4-fluorobenzenepropanoic acid, ethyl ester

– **63**. CAS 129586329: SSF-109 fungicide

– **64**. CAS 131983727: triticonazole

– **65**. CAS 139528851: metosulam

– **66**. CAS 147150354: cloransulam

Bhhatarai and Gramatica [1] go on to state that "[t]riazoles are amphoteric in nature, acting as both acids and bases. However, benzotriazoles are basic, pK_a=8.2, and weakly polar in nature. These properties make them very soluble in polar solvents such as water, with a moderate tendency towards partition [sic] in the organic phase. (Benzo)triazoles are often present and persist in the water compartment, and can thus be toxic to aquatic organisms. Their resistance to oxidation under ambient conditions and their UV stability allows them to be persistent in the biota for long periods." Since 90% of the training set compounds used by Bhhatarai and Gramatica [1] do not appear to be benzotriazoles, these general assumptions do not appear to generally apply to the compounds they are studying. This is particularly important for the acid/base character of their training set compounds, since pK_a has a substantial effect on solubility and the partitioning behavior between water and other phases such as air and octanol.

The pK_a values of the compounds Bhhatarai and Gramatica [1] employ in their training set do not appear to all be about 8.2 (in contrast to the assumptions of these authors). Rather, a number of compounds (e.g., **5**, **16**, **29**, **35**, **40**, and **58**) appear to have pK_a values at near neutral pH, suggesting that they will be substantially - if not effectively entirely - ionized under environmentally relevant conditions.

Similar problems exist in the set of 351 purported benzotriazoles for which Bhhatarai and Gramatica [1] attempt to predict the physico-chemical properties and screen the partitioning behavior using their QSPR model. A substantial number of these compounds are not benzotriazoles and do not have similar properties as benzotriazoles. Consequently, it appears that the approach, assumptions, and results in the work of Bhhatarai and Gramatica [1] must be viewed as potentially fundamentally flawed.

References

[1] B. Bhhatarai, P. Gramatica, Modelling physico-chemical properties of (benzo)triazoles, and screening for environmental partitioning, Water Research 45 (2011) 1463–1471.