Molecular Docking Studies and N Design,Synthesis,Characterization of Benzimidazole Containing 4h-Chromen-4-One Derivatives and It's Biological Evaluation

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Abstract: Molecular docking is a computational technique that predicts the binding affinity of ligands to receptor proteins. Although it has potential uses in nutraceutical research, it has developed into a formidable tool for drug development. The limitations and difficulties of using molecular docking in nutraceutical research are also covered, including the reliability of scoring functions and the requirement for experimental validation The reaction conditions to produce precursor dimetho Xy-substituted benzo [4,5] imidazo [1,2-*a*]- imidazo [1,2-*c*] pyrimidine-6,9-diones. In contrast to many synthetic methods for other N-fused hybrids, limited examples for the synthesis of such N-fused hybrid sca*ff*olds A and B are known. It is reported that N-fused hybrid old A can be synthesized by the reaction of 2- aminopyrimidine with *p*-chloranil (2,3,5,6-tetrachloro-1,4-benzoquinone) followed by subsequent treatment with diethylamine and HCl. We reported on the synthesis of N-fused hybrid sca*ff* old B by step-by-step copper-catalyzed coupling a cyclization 2-(2-bromovinyl)- 4,7- dimetho Xy benzimidazoles with primary amides to form pyrimidine-fused 4,7-dimethoXybenzimidazoles, and Oxidation pyrimidines of N-fused hybrid sca*ff*old A e*ff*ectively.

Keywords: Docking software, Nutraceutical, Molecular Descriptors, Perkin Elmer Spectrum, DMSO.

INTRODUCTION

Drug discovery and development process

Drug discovery and development process is one of the most challenging and difficult process because this process is often a matter of life and death for patients; their cures are in the hands of scientists and clinicians who discover, develop,[1] and administer medications for prevention, management, and cure of disease, injuries, and other disorders. But it takes about 12 - 15 years from discovery to the approved medication and requires an investment of about billion dollars.[2]

Molecular Descriptors used in QSAR

Molecular descriptors can be defined as a numerical representation of chemical information encoded within a molecular structure via mathematical procedure.[3] This mathematical representation has to be invariant to the molecule's size and number of atoms to allow model building with statistical methods.[4]

The information content of structure descriptors depends on two major factors:

(1) The molecular representation of compounds.

(2) The algorithm which is used for the calculation of the descriptor.

Molecular Docking

When the structure of the target is known (available), usually from X-ray crystallography, the most commonly used virtual screening method is molecular docking.[5] Molecular docking can also be used to test possible hypotheses before conducting costly laboratory experiments. Molecular docking programs try to predict how a drug candidate binds to a protein target without performing a laboratory experiment. Molecular docking software consists of two core components. An evaluation function (sometimes called a score function).[6] This is a function providing a measure of how strongly a given ligand will interact with a particular protein. Energy force fields are often used as evaluation functions.[7] These force fields calculate the energy contribution from different terms such as the known electrostatic forces between the atoms in the ligand and in the protein, forces arising from deformation of the ligand, pure electron-shell repulsion between atoms and effect from the solvent in which the interaction takes place.[8] An

example of a drug candidate (grey color) binding to a target (black color). The small filled circles represent solvent (water) molecules.[9]

Materials and methods

All the chemicals were purchased from sigma chemicals Raipur C.G. Analytical TLC was performed on Precoated sheets of silica gel G/UV-254 of 0.2mm thickness using analytical grade solvent and visualized with iodine spray (10% w/w I2 in silica gel) or UV light. We also used bioinformatics tools, biological databases like PDB (Protein Data Bank) and software's like Autodock and ACD ChemSketch.[10] The PDB (Protein Data Bank) is the single worldwide archive of Structural data of Biological macromolecules, established in Brookhaven National Laboratories (BNL). It contains Structural information of the macromolecules determined by X-ray crystallographic, NMR methods etc.[11] Auto Dock is an automated docking tool. It is designed to predict how small molecules, such as substrates, bind to a receptor of known 3D structures. Argus lab also one of the automated docking tool.[12]

Equipment and analytical instrument

Melting point was determined in capillary tubes and is uncorrected. IR spectra were taken as KBr pellets for solids on Perkin Elmer Spectrum FT-IR. 1H NMR (400MHz) and 13C NMR (100 MHz) spectra were recorded in DMSO-d6 solution with TMS as an internal standard on Bruker instrument. Spin multiplicities are given as s (singlet), d (doublet), t (triplet) and m (multiplet).[13]

Coupling constant (J) is given in hertz. Mass spectra were recorded on a thermo Finnigan LCQ Advantage MAX 6000 ESI spectrometer.

General procedure for the synthesis of title compounds[14]

Step 1: Synthesis of 2-methyl-1H-benzo[d]imidazole

1. Place 5.43g of o-phenylene diamine, 20ml of water and 5.4g of acetic acid in RBF.
2. Reflux in a water bath for 45 minutes.
3. Cool and add 10% ammonia solution slowly with constant shaking.
4. Filter the precipitated product.
5. Recrystallise it from 10% aqueous ethanol and activated charcoal.

Synthesis of Ethyl-[2-n-butyl-2-hydroxy methyl] hexanoate (29)

Diethyl di-n-butyl malonate (25 g, 0.09 mol) was dissolved in toluene (142.8 ml) under N2 atmosphere and cooled to -60 to -70oC. DIBAL-H (25% in toluene, 31.32 g, 0.22 mol) solution was added at this temperature for 4 h, stirred for 15min. Absolute ethanol (176.76 ml) was added slowly at -40 to -50 oC and the temperature was raised to 0 oC. NaBH4 (3.49 g, 0.09 mol) was added portion wise below 0 oC and the reaction mixture was stirred at room temperature for one hour, cooled to 15 – 20 oC and saturated Na2SO4 solution was added. The reaction mass was stirred for an hour, filtered through celite bed, extracted with ethyl acetate (25×2), washed with brine, dried over sodium sulfate and concentrated under vacuum at 50-55 oC to afford the title compound 29 as thick syrup. NMR (400MHz, DMSO-d6): δ = 4.56(t, 1H, J=4.8), 4.01(q, 2H, J=7.2), 3.42(d, 2H, J=5.2), 1.36-1.49(m, 8H), 1.18(t, 4H, J=7.2), 0.80(t, 6H, J= 8.6); 13C NMR (100MHz, CDCl3): δ = 13.83, 22.86, 25.98, 34,08, 36.13, 50.20, 181.07; MS (ES) m/z (m+1) :

244.3

Synthesis of Ethyl-[2-n-butyl-2-hydroxy methyl hexanoic acid (30)

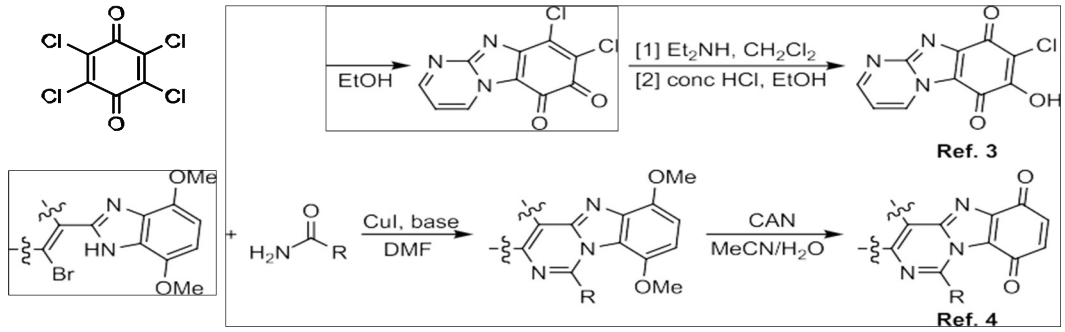
To a stirred solution of Ethyl-[2-n-butyl-2-hydroxy methyl] hexanoate (15 g, 0.0652 mol) in methanol (67.5 ml), NaOH (5.86 g, 0.146 mol) solution was added and refluxed for 17h. Distilled off the methanol at 55-60 oC under vacuum, cooled to room temperature and washed with petroleum ether. Aqueous layer was taken back to the reactor, cooled to 10-15 oC and acidified with concentrated HCl to get pH 2. Extracted with dichloromethane (25×2) and washed with brine solution. Organic layer was dried over sodium sulfate and concentrated under vacuum at 40 – 45 oC to yield thick syrup. Pale yellow liquid, yield 13.73, 92%; FT-IR(Paraffin) υ/cm-1 : 2857, 3359, 2857; 1H NMR (400MHz, DMSO-d6): δ = 11.94(s, 1H), 3.40(d, 2H, J=4.8), 1.34-1.46(m, 8H), 1.24(t, 4H, J=7.2), 0.80(t, 6H, J= 8.6); MS (ES) m/z(m+1) 203.3.

RESULTS AND DISCUSSION

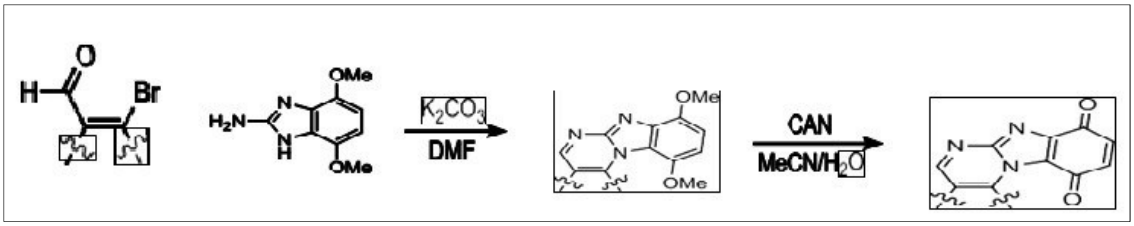
The reaction conditions to produce precursor dimetho Xy-substituted benzo [4,5] imidazo [1,2-a]- imidazo [1,2-c] pyrimidine-6,9-diones. In contrast to many synthetic methods for other N-fused hybrids, limited examples for the synthesis of such N-fused hybrid scaffolds A and B are known. It is reported that N-fused hybrid old A can be synthesized by the reaction of 2-

aminopyrimidine with p-chloranil (2,3,5,6-tetrachloro-1,4-benzoquinone) followed by subsequent treatment with diethylamine and HCl. We reported on the synthesis of N-fused hybrid scaff old B by step-by-step copper-catalyzed coupling a cyclization 2-(2-bromovinyl)-4,7- dimetho Xy benzimidazoles with primary amides to form pyrimidine-fused 4,7-dimethoXybenzimidazoles, and Oxidation pyrimidines of N-fused hybrid scaffold A effectively. On the basis of recent reports on transition metal−free cyclocondensation of β-bromo-α,β-unsaturated aldehydes and 2- halobenzaldehydes with 2-aminobenzimidazole,7,9 shows several attempted results for the cyclocondensation of 2-bromocyclohex- 1-enecarbaldehyde (1a) with 4,7-dimethoXy- 1H-benzo[d]imidazole-2-amine (2a) under various reaction conditions, leading to 8,11-dimethoXy-1,2,3,4-tetrahydrobenzo-[4,5] imidazo [1,2-a]quinazoline (3a). The starting 2a was Synthesis of Benzo [4,5] imidazo [1,2-a]pyrimidine-6,9-diones A and Benzo [4,5] imidazo [1,2-c]pyrimidine-6,9-diones B contrast to the reaction between β-bromo-α,β-unsaturated aldehydes and 2-aminobenzimidazoles, further addition of magnesium sulfate resulted in rather decreased yield of 3 entry 8). The reaction also proceeded in the presence of other inorganic bases such as K3PO4, NaOBu, NaOAc, Cs2CO3, and CsF, but the yields of 3a were generally lower than that obtained in the presence of K2CO3 entries 9−13. Unlike the previous cyclo condensation of β- bromo-α,β-unsaturated aldehydes and 2- amino benzimidazoles, no allowable yield of 3a was observed with Et3N entry 14). When 1a was treated with 2a under usual heating conditions (screw-capped vial) for 10 h, 3a was obtained in 52% yield. Having optimized the reaction conditions, various β-bromo- α,β-unsaturated aldehydes 1 were subjected to the reaction with 2 a to investigate the reaction scope, and several representative results are summarized in the cyclocondensation of 2-bromocyclohex-1-enecarbaldehydes (1b and 1c) with 2a also proceeded to give the corresponding pyrimidine-fused benzimidazoles (3b and 3c) in similar yields, irrespective of the presence of the methyl and phenyl substituents on 1b and 1c. With cyclic β-bromo-α,β- unsaturated aldehydes 1d−f having various ring sizes, the corresponding N-fused scaffolds 3d−f were also formed in 72−a1a (0.3mmol), base (0.9mmol), additive (0.6mmol), microwave irradiation (100 W initial power),DMF (3 mL), unless otherwise stated. Further addition of MgSO4 (0.6 mmol).

Under usual heating (screw-capped vial). prepared from 3,6-dimethoXybenzene-1,2-diamine[2b,10] and cyanogen bromide using similar methods reported.[11] Treatment of 1a with equimolar amount of 2a in dimethyl formamide (DMF) at 110 °C for 1 h in the presence of K_2CO_3 under microwave irradiation a*ff*orded 3a in 64% isolated yield entry 1.



The molar ratio of 2a to 1a, although not signi*fi*cant, a*ff*ected the yield of 3a, and the yield increased with the increase in the molar ratio up to 1.2 without other identi*fi*able by-products (entries 1−3). Lower yield of 3a was observed under lower reaction temperature, and the yield increased with the increase in temperature up to 110 °C. 82% yields. The reaction of benzo-fused *β*-bromo-*α*,*β*- unsaturated aldehydes 1g took place with 2a to give 8,11- dimethoXy-13,14-dihydrobenzo [*f*] benzo [4,5] imidazo [1,2-*a*] quinazoline (3g) in 21% yield along with its dehydrogenated product 3g′ (35% yield). Performing the reaction for prolonging reaction time (2 h) under the employed conditions solely a*ff*orded 3g′ in 61% yield. This result indicates that 3g′ is produced by dehydrogenation of 3g initially formed by the cyclization of 1g. Such a similar dehydrogenation was observed by our recent reports on coupling and cyclizaton reactions using similar benzo-fused six-membered ring substrates. Acyclic *β*-bromo-*α*,*β*-unsaturated aldehydes 1h−o having alkyl and aryl substituents were also cyclocondensed with 2a to a*ff*ord pyrimidine-fused benzimidazoles 3h−o in 55−67% yields and the product yield was not signi*fi*cantly a*ff*ected by the identity of such substituents. Similar treatment of 2-bromobenzaldehydes (1p and 1q)with 2a under the employed conditions produced the corresponding quinazoline-fused benzimidazoles (3p and 3q)



Refference

1. B. V. S. Kumar, S. D. Vaidya, R. V. Kumar, S. B. Bhirud, R. B. Mane, European J. Med. Chem. 41 (2006) 599–604.
2. C. Dyrager, L. Nilsson, L. Karlsson K. J. Patrick Alao, D. Peter,K. F. Wallner, P. Sunnerhagen, and M. Grotli, J. Med. Chem., 2011, 54, 7427–7431.
3. D. Gree, S. Vorin, V. L. Manthati, F. Caijo, G. Viault, F. Manero, P. Juin and R. Grée, Tetrahedron Lett., 2008, 49(20), 3276-3278.
4. D. Pascual, R. Giron, A. Alsasua, B. Benhamu, M. L. Lopez-Rodrıguez, M. I. Martin, European J. Pharmacology 462 (2003) 99-107.
5. E. P. Jesudason, R. Jayakumar, S. K. Sridhar, E. J. Padma Malar, P. Shanmugapandiyan, M. Inayathullah, V. Arul, D. Selvaraj, European J. Med. Chem. 44 (2009) 2307-2312.
6. G. Ayhan-Kılcıgil, N. Altanlar, Il Farmaco. 58 (2003) 1345-1350.
7. Mohammadpoor-Baltork, A. R. Khosropour, S. F. Hojati, Catal. Commun. 8 (2007) 1865– 1870.
8. Imran Ali, A. Waseem, Wani and Kishwar Saleem, 2011, Cancer Therapy., 8, 56.
9. J. F. Swinbourne, H. J. Hunt and G. Klinkert, Advances in Het. Chem., 1987, 23, 103-170.
10. Rakesh Tiwle “An Exhaustive Review On Solubility Enhancement For Hydrophobic Compounds By Possible Applications Of Novel Techniques.” Science Alert –Trends Research In Applied Science And Research. 7(8): 596-619; 2012.
11. J. M. Batista, A. A. Lopes, D. L. Ambrósio, L. O. Regasini, M. J. Kato, V. da Silva, R. M. Barretto, and M. Furlan, Biol. Pharm. Bull.,2008, 31, 538—540.
12. J. M. Batista, A. A. Lopes, D. L. Ambrósio, L. O. Regasini, M. J. Kato, V. da

Silva, R. M. Barretto, and M. Furlan, Biol. Pharm. Bull.,2008, 31, 538—540.

13. J. V. Greenhill, A. R. Katritzky and C. W. Rees, Eds., Pergamon Press, 1984, 5, 302.
14. M. A. Messmary, M. G. Elarfi, R. Mohamed, Int. J. ChemTech Research. 2 (2010) 1714- 1716.
15. Rakesh Tiwle, Effect of PH of AlCl3 Solution on Drug Entrapment Efficiency of IPN Beads, International Journal of Chemistry and Pharmaceutical Sciences, IJCPS, 2014, Vol.2(6): 878-881.