International Journal of Chemistry and Applications.
ISSN 0974-3111 Volume 5, Number 4 (2013), pp. 257-265

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Virtual Screening and Evaluation of of 4-(2-bromo naphthalene-6-yl) -6-phenylpyrimidin-2-amine

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Abstract

A series of 4-(2-bromonaphthalene-6-yl)-6-phenylpyrimiidin-2-amines have been synthesized and screened for drug likeness property using Lipinski's rule of five. Among 6 compounds three compounds were further evaluated for the conformation based molecular docking studies using lib dock. The corticotrophin releasing factor (CRF) signaling system plays an essential role in initiating autonomic responses to stress. Hence inhibiting the CRF Receptor 1 (CRF-R1) pathway, stress-induced tau phosphorylation is eliminated. Thus from Insilco studies aromatic amino acid present in the active site of the protein favors the interaction with the compounds; in particular the ARG residues are more prominent binding with the compounds. So in future this kind of compounds can be used for the inhibiting the CRF Receptor 1 for neuron based diseases.

Key words: 4-(2-bromonaphthalene-6-yl)-6-phenylpyrimiidin-2-amines, Lipinski's rule, docking

1. INTRODUCTION

Cheminformatics is the use of computer and informational techniques, applied to a range of problems in the field of chemistry. These Insilco techniques are used in pharmaceutical companies in the process of drug discovery. The term theoretical chemistry may be defined as a mathematical description of chemistry, whereas computational chemistry is usually used when a mathematical method is sufficiently well developed that it can be automated for implementation on a computer. In theoretical chemistry, chemists, physicists and mathematicians develop algorithms

and computer programs to predict atomic and molecular properties and reaction paths for chemical reactions. Computational chemists, in contrast, may simply apply existing computer programs and methodologies to specific chemical questions.

There are two different aspects to computational chemistry:

- Computational studies can be carried out to find a starting point for a laboratory synthesis, or to assist in understanding experimental data, such as the position and source of spectroscopic peaks.
- Computational studies can be used to predict the possibility of so far entirely unknown molecules or to explore reaction mechanisms that are not readily studied by experimental means.

Thus, computational chemistry can assist the experimental chemist or it can challenge the experimental chemist to find entirely new chemical objects.

Several major areas may be distinguished within computational chemistry:

- The prediction of the molecular structure of molecules by the use of the simulation of forces, or more accurate quantum chemical methods, to find stationary points on the energy surface as the position of the nuclei is varied.
- Storing and searching for data on chemical entities.
- Identifying correlations between chemical structures and properties.
- Computational approaches to help in the efficient synthesis of compounds.
- Computational approaches to design molecules that interact in specific ways with other molecules (e.g. drug design and catalysis)

2. Experimental section

2.1. MATERIALS AND METHODS

All the chemicals used were reagent grade and were used as received without further purification unless noted. Melting points are determined using open capillary and are uncorrected. The ^{1}H and ^{13}C NMR spectra were recorded on Broker (AMX-400) using DMSO-d6 as solvent and TMS was used as internal reference. The chemical shifts are in parts per million (ppm). Mass spectra were recorded on CLASS-5000 mass spectrometer. Elemental analysis was done on vario. EL.CHNOS elemental analyser.The IR spectra were recorded on Shimadzn-FT.IR spectrometer. The bromine substituted aminopyrimidiine have been synthesized by expecting some more bioactivities against microorganism since the very potent bioactive nature of bromine.

The NMR spectra of all the synthesized compounds have conformed the structure of Aminopyrimidine in addition with the evidences obtained from IR, mass and elemental analysis (Table-1). The physical parameters like TLC and melting points (table-1) of synthesized compounds are quite different from starting materials also support the pyrimidine formation.

The 1HNMR spectra of compounds 4a-f, having the characteristic signal for amino protons at the chemical shift value (∂ppm) of 6.7-6.9(2H, S) and was

confirmed by the addition of D_2O, results the disappearance of respective peak at particular chemical shift range, the proton present in the fifth position (H-5) of pyrimidine ring appears around 8.5-9.00 ppm (1H, S) and the aromatic protons are in the region around 7.3-8.4 ppm as multiplets.

The ^{13}CNMR displays characteristic peaks at ∂ (ppm) 100-106(C-5) and 163-165(C-2, C-4 and C-6).The IR spectra of compounds shows the characteristics bands (Cm^{-1}) corresponding NH-stretching (3300-3500), C=C- stretching(1400-1450), C=N-stretching(1550-1570), C-NH2 stretching(1300-1400) and C-Br stretching(650-700).The mass spectra of compounds 4a and 4b show the corresponding fragmented ions and molecular ions peaks, M^+(376 and 410), M^{+2}(378, 412) and base peaks(101 and 79).

2.2. Procedure for preparation of 1-(2-bromonaphthalene-6-yl) ethanone.

A mixture of 2-bromenaphthalene (41.5g, 0.2mol) and anhydrous aluminum chloride (70g, 0.5mol) in nitrobenzene (250ml) were taken in a one-liter three necked flask with condenser carrying a guard tube and a dropping funnel. The reaction mass was cooled to 10-20 and about 31.2g (0.4mol) of acetyl chloride was added during 30 minutes through the dropping funnel with stirring. The stirring was continued for another 3 hours. After the removal of nitrobenzene by steam distillation the reaction mass was poured to ice water (250ml) containing 50ml of HCl and the product was separated by filtration and purified by the Literature procedure.

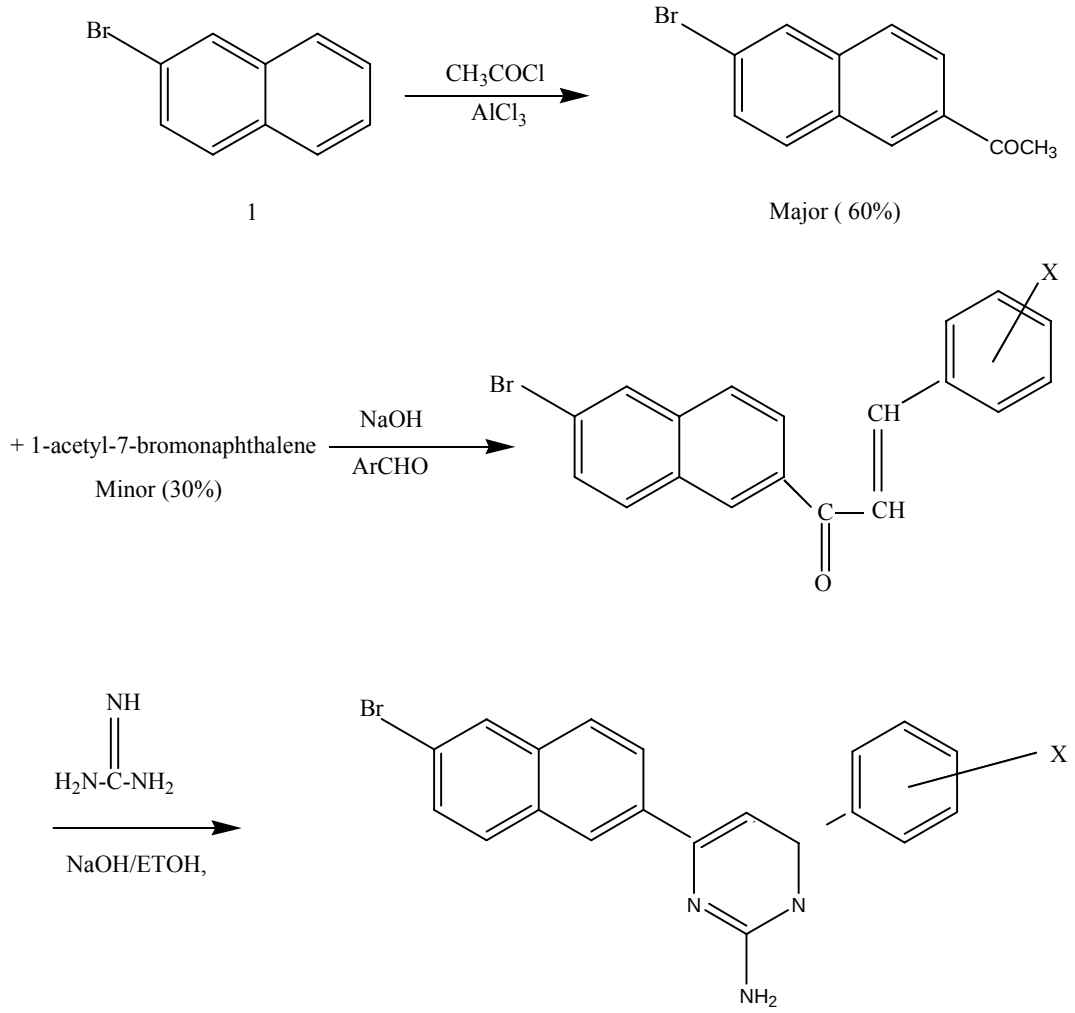
2.3. General procedure for preparation of 1-(2-bromonaphthalene6yl)-3-arylprop-2-en-1-ones (3a-f).

Quantitative amount of the substituted aromatic aldehyde (0.02mol) and 1-(2-bromonaphthalene-6-yl) ethanone (0.02mol) in ethanol(50ml),were heated over a water bath while a solution of sodium hydroxide (1.5g/5ml of water) was added slowly during 15 minutes and the heating was continued further 15 minutes. The solution was cooled, filtered the product and re-crystallized from ethanol.

2.4. General procedure for preparation of 4-(2-bromonaphthalene-6-yl)-6-phenyl pyrimidin-2-amine (4a-f).

A solution containing 1-(2-bromenapthalen-6-yl)-3-arylprop-2-en-1-one (0.01mol), guanidine nitrate (0.01mol) and ethanol (50ml) was refluxed. To that sodium hydroxide solution 2g/10ml water was added portion wise for 2 hours. The refluxing was continued for further 4-5 hours and checked TLC for reaction completion. After that one third of the solvent was removed under reduced pressure, cooled to room temperature, poured to ice cold water and filtered the solid product. The pure 2-aminopyrimidines were obtained from column chromatographic technique using benzene-Ethyl acetate as solvent.

Scheme:



3. Results and Discussion

Lead identification or optimization is the one of the most important steps in drug development. The chemical structure of the lead compound is used as a starting point for chemical modifications in order to improve potency, selectivity, or pharmacokinetic parameter. For the drug likeness property the lead compounds should follow the Lipinski's rule 5.

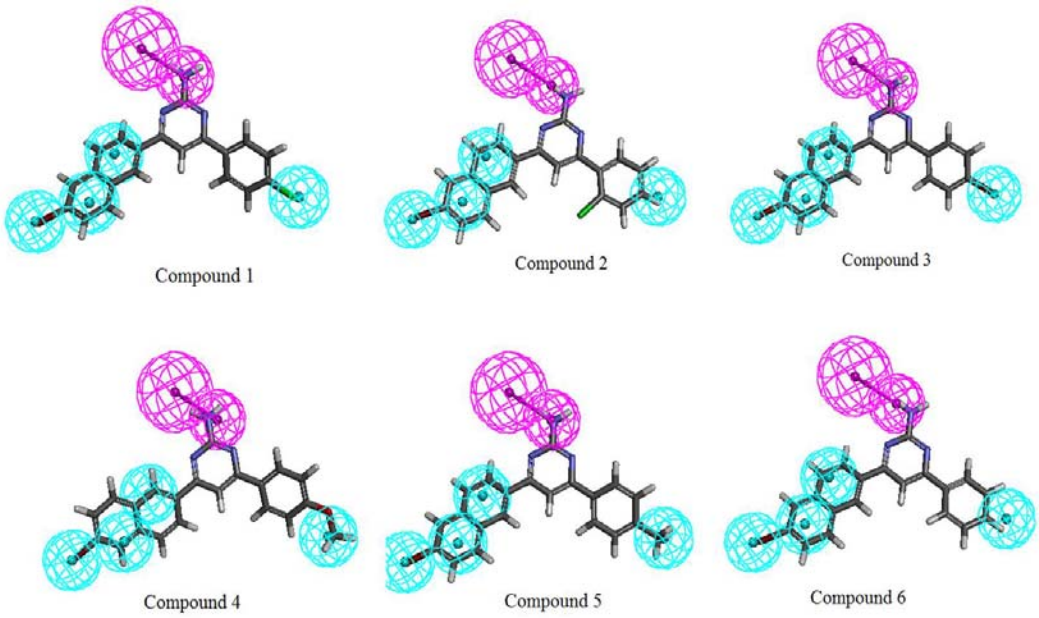
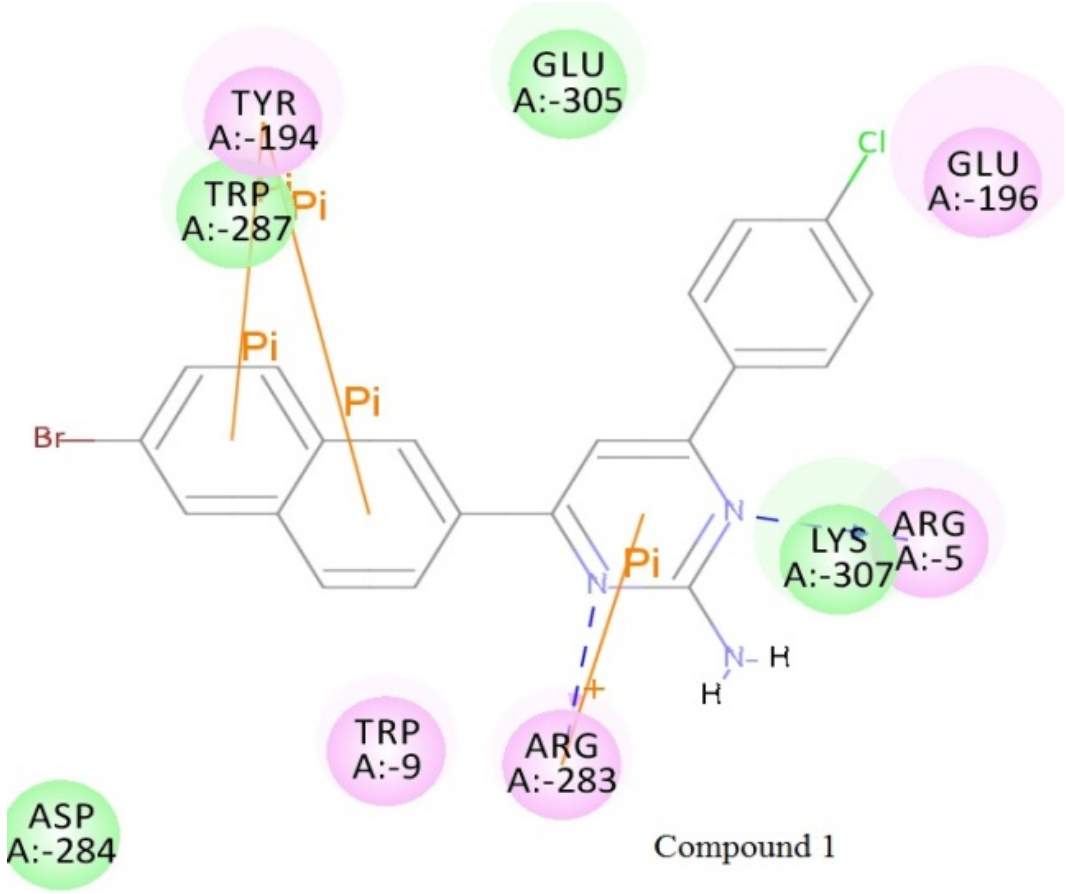


Figure 1: Compound 1-6

Lipinski's Rule of Five is a rule of thumb to evaluate druglikeness or determine if a chemical compound with a chemical or biological activity has properties that would make it a likely orally active drug in humans. [20] From the above table 1 the Alog p value is more than 5 indicated the compound is too hydrophobic in nature and all compounds shows the molecular weight less than 500 and HBA (Hydrogen bond acceptor) are less than 10 and HBD are less than 5,except Partition coefficient other properties of Lipinski's properties are obeyed.



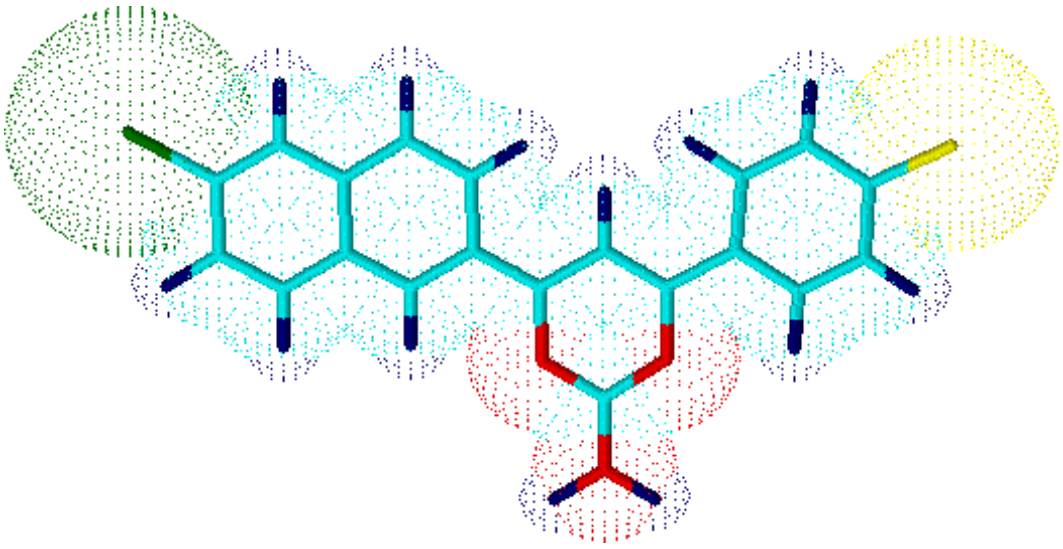
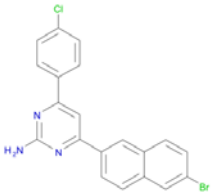
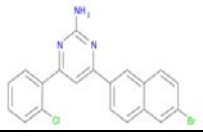
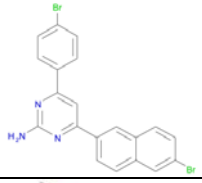
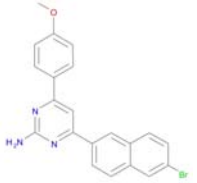
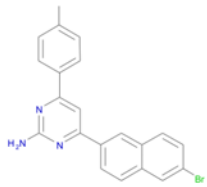
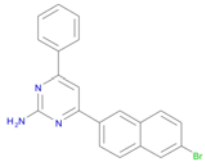


Figure 2: The Binding site of the protein

Table 1: Calculation of Molecular Properties of the lead compound

Compounds	Structure	ALogP	Molecular Weight	HBA	HBD
1		6.04	410.694	3	1
2		6.04	410.694	3	1
3		6.124	455.145	3	1
4		5.359	406.275	4	1
5		5.862	390.276	3	1
6		5.376	376.249	3	1

3.1. 4-(2-bromonaphthalen-6-yl)-6-phenylpyrimidin-2-amine.
^{1}H NMR,∂(ppm) 6.83 (2H,S,NH_2),8.85(1H,S,H-5),7.54-8.41 (Ar-H).^{13}C NMR, ∂ (ppm) 102.18 (C-5), 164.02 (C-4), 164.33 (C-6), 165.01 (C-2) and120.47-137.22 (Ar-C).Mass,m/z 376 (M^+),378 (M^++2), Base peak 103 $C[C_5H_5CN]^{+\cdot}$

3.2. 4-(2-bromonaphthalen-6-yl)-6-(2-chloro phenyl) pyrimidin-2-amine.
^{1}H NMR, ∂(ppm) 6.89 (2H,S,NH_2),8.75(1H,S,H-5), and 7.47-8.28 (Ar-H).^{13}C NMR,

∂ (ppm) 106.45 (C-5), 163.55 (C-4), 163.84 (C-6), 165.86 (C-2) and 120.56-137.91 (Ar-C).Mass,m/z ,410 (M^+),412 (M^++2), Base peak 79 $C[C_4N_2H_3]^{+\cdot}$

3.3. 4-(2-bromonaphthalen-6-yl)-6-(4-chloro phenyl) pyrimidin-2-amine.
^{1}H NMR, ∂ (ppm) 6.85 (2H,S,NH_2),8.82(1H,S,H-5),7.58-8.39 (Ar-H).^{13}C NMR, ∂(ppm) 102.08 (C-5), 163.67 (C-4), 163.99 (C-6), 164.56 (C-2) and 120.49-136.06 (Ar-C).Mass,m/z 376 (M^+),378 (M^++2), Base peak 103 $C[C_5H_5CN]^{+\cdot}$

3.4. 4-(2-bromonaphthalen-6-yl)-6- (4-methoxyphenyl) pyrimidin-2-amine.
^{1}H NMR, ∂ (ppm) 6.72 (2H,S,NH_2),8.82(1H,S,H-5), 3.84(3H,S,-OCH_3) and 7.54-8.39 (Ar-H).^{13}C NMR, ∂(ppm) 101.42 (C-5), 163.89 (C-4), 163.99 (C-6), 55.30 (OCH_3), 164.53.(C-2) and 120.37-145.66 (Ar-C).

3.5. 4-(2-bromonaphthalen-6-yl)-6- (4-nitrophenyl) pyrimidin-2-amine.
^{1}H NMR, ∂(ppm) 6. 31 (2H, S, NH2), 8.58(1H, S,H-5), and 6.41-8.13 (Ar-H).^{13}C NMR, ∂ (ppm) 100.50 (C-5), 163.33 (C-4), 163.78 (C-6), 165.15 (C-2) and 120.23-135.76 (Ar-C).

3.6. 4-(2-bromonaphthalen-6-yl)-6- tolylpyrimidin-2-amine.
^{1}H NMR, ∂ (ppm) 6.75 (S,2H,NH_2),8.83(1H,S,H-5), 2.38 (3H,S,-CH_3) and 7.33-8.39 (Ar-H).^{13}C NMR, ∂ (ppm) 101.83 (C-5), 163.99 (C-4), 164.17 (C-6), 164.88 (C-2),20.92 (-CH_3) and 120.40-140.31 (Ar-C).

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