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Design, synthesis of novel pyrazolopyridine derivatives and CREBBP bromodomain inhibitors docking and molecular dynamics

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A sequence of novel compounds pyrazolopyridine have been prepared by a general synthetic method. Due to high efficiency and selectivity, anticancer agents consisting of combined molecules have gained great interests. The IC50 values have been determined against cell line U937, the results obtained indicate the potential effects against cancer cell line. The cell potency of cell line is best for compounds **4a** IC50 = 62.5 μM, **5b** IC50 = 62.5 μM,**4b** IC50 = 31.2 μM, **4e** IC50 = 31.2 μM), selectivity and *in vivo*. Further, the molecular docking studies indicate that substituted pyrazolo[4,3-c]pyridine derivatives show good anticancer activity in the medicinal field. The ease of synthesis and the significant biological activities make these compounds potential new frameworks for progress of cancer therapeutics. Compound **4f** shows anticancer effect in cancer cell lines and *in vivo* that corresponds with antitumor activity in an AML cancer type. For the molecular docking with the ligands, the RMSD value has been calculated, the protein with the least RMSD is found to be 5KTU screening with 20 small molecules.

Keywords: Pyrazolopyridine, anti-cancer, bromodomains, molecular dynamics

Worldwide, cancer is the most commonly diagnosed malignancy leading to deaths[1]. Chemical modification of biologically active compounds of natural origin is one of the most efficient approaches in drug development. Pyrazolopyridine is a potent class in heterocyclic compounds which possess a wide spectrum of biological activities[2]. The bromodomains of CBP/EP300 are targeted in transcriptional regulators factor in human cancer immunotherapy[3]. The BET family are inhibition of bromodomains is exposed to have probable therapeutic advantage in cancer, inflammation, immunology[4]. Acetyl Lysine modifications in proteins is recognition that Bromodomains are involved in transcriptional regulation. Highly discerning inhibitor of the CREB binding protein (CBP) bromodomain and its exploit in cell-based transcriptional application. For the gene regulation CBP and p300 (CREBBP or KAT3A and EP300 or KAT3B) are used two major HATs[6]. In Cell biology T cell regulation of the CREBBP/EP300 bromodomains have a major role and T Cells are used in cancer immunotherapy[7]. Post translational change in the function of bromodomains in protein molecules in acetylated lysine on histones, important functions[8]. The CREBBP Bromodomain ligands with cation π interaction are useful tools[9]. Pyrazolopyridines are interrelated with DNA and inhibit growth of cancer cell lines[10]. For non-BET bromodomain have the proteins have been used in the HIV and cancer diseases chemical Probes potentially lead to drug discovery[11]. Bromodomains that have the domains are BCPs, HATs and HDAC are effectively used in cancer therapy[12]. BET bromodomain has reflective anticancer and anti-inflammatory in the chemical probes used in biological observed compounds in clinical trials[13]. The CREBBP bromodomain binds to KAc382 in human cancer with p53 and acetylation-dependent and DNA damage[14]. The BET family has the schoffled bromodomain BRD2, BRD3, BRD4 are binding specificity very strong and prospective therapeutic benefit[15]. The CBP/p300 bromodomains are used in regulators of cell growth acetyl-lysine protein inhibitor[16]. The oncogenic fusion in leukemia is a MOZ acetyl transferees to detect CBP/p300 domain[17,18]. The AML1-ETO fusion protein interacts with p300 and transcription regulates in AML1–ETO aim gene inhibitor of DNA binding[19]. Screening of a small molecular library identifies the compound interaction of p 53 and KAc382-CREBBP at 100 and 50 μM respectively[20]. For the novel male

contraceptives is a first bromodomain of BRDT-1 is for male germ cell differentiation used and c-Myc-dependent cancers[21].

In BRD4 activation of the tumor in the micro level *in vivo*, the reduction of tumor growth and pulmonary of the metastasis in mice and human BRDs in chromatin biology and gene transcription[22]. Here we are report the development of a pyrazolopyridine based series of compounds, showing the silico discovery of CREB binding protein and bromodomain and efficacy towards antitumor activity (Figure 1).

Molecular docking plays an important role of small molecule to their target protein in order to discover its affinity and activity its binding site[23]. Molecular dynamics simulations as tool as of medicinal chemistry has been successfully used for design of biologically active to identify antitumor activity, including inhibition and stability[24]. In this study microsecond molecular simulation is used to binding site of RVX-208 with bromodomain of BET proteins[25]. Molecular dynamics are ligand design focused on the potential molecule for the CBP bromodomain and high selectivity[26].

Results and Discussion

In general, the yields of the synthesis were quite good and reasonable quantities of the materials were easily available. Although this general synthetic route was used for the synthesis of most of the analogues, other methods could be used for specific substitution patterns and will be given in the Experimental Section. The compounds were purified by normal synthetic medicinal chemistry means, usually column chromatography, and their structures were determined by high field NMR spectroscopy. The starting aldehyde, ketone required for further transformation were prepared by claisen-schmidt condensation.

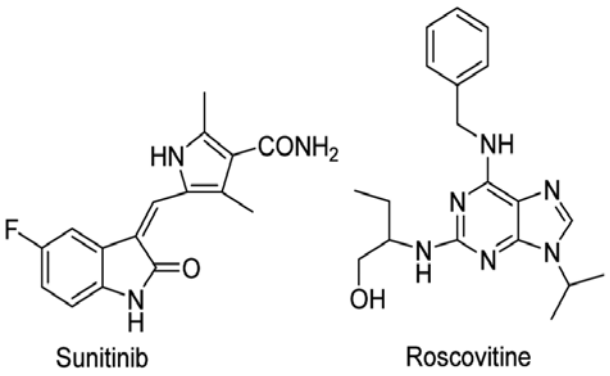


Figure 1 — Potent anticancer compounds

Synthesis of substituted chalcones

A mixture of substituted aldehydes (0.02 mol) and 1-methyl-4-piperidone (0.01 mol) in the presence of 10% NaOH along with 50 mL ethanol was prepared and the solution of reaction mixture was constant stirring for 15hrs at RT of stirring the solution was poured in to ice cubes to enhance the precipitation. The precipitate was then collected and washed with distilled water for draining excess sodium hydroxide from the product **3a**[1-10]. The compound is purified and recrystallized with ethanol (Scheme I).

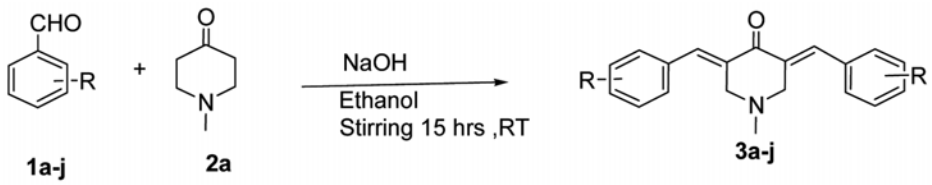
Synthesis of substituted pyrazolo pyridine derivatives

Equal moles of substituted chalcone and semicarbazide hydrochloride with 10% sodium hydroxide were refluxed at 80°C in a heating mantle for 6 hr produced, substituted pyrazolopyridine **4a**[1-7]. All the compounds were purified by recrystallization from ethanol (Scheme II).

Computational details

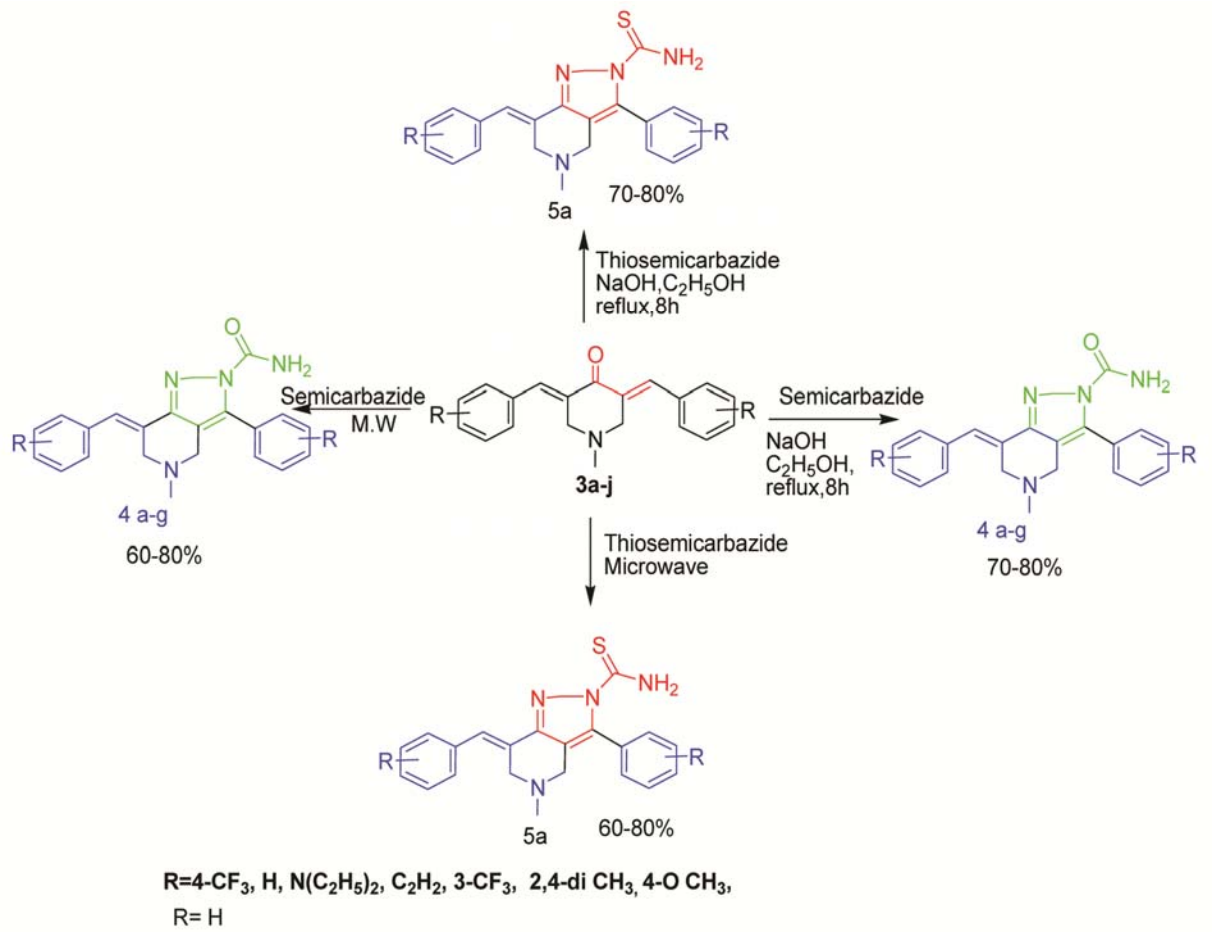
Docking results

For medicinal chemistry to discover the drug molecule to identify novel drug molecular docking technology. The molecular docking studies are to specify best ligand interaction and stable molecule[27]. To dock, 20 structures of ligands have been determined. Meanwhile, these ligands were used to conduct native docking to measure the



R=H,2,6di Cl-4-CH_3,C_5H_7S,N(C_2H_5)$_2$,N(CH_3)$_2$,4-CF_3,C_2H_2,3-CF_3,4-OCH_3, 2,4-di CH_3

Scheme I



Scheme II

Table I — Glide Docking and binding energy scores

Compd	docking score	Glide gscore	Glide emodel	XP GScore	Glide energy	Glide emodel
5KTU	-6.612	-6.612	-6.612	-6.612	-42.057	-59.809
4a	-6.237	-6.237	-6.237	-6.237	-35.312	-49.981
5a	-5.98	-5.98	-5.98	-5.98	-34.8	-49.39
4d	-5.572	-5.572	-5.572	-5.572	-31.043	-47.634
4b	-5.468	-5.468	-5.468	-5.468	-31.746	-40.129
4f	-4.96	-4.96	-4.96	-4.96	-26.952	-39.954
4e	-4.032	-4.032	-4.032	-4.032	-31.793	-45.413
4c	-3.946	-3.946	-3.946	-3.946	-34.717	-48.26

docking conformations. Three different docking programs SP Glide, and XP Glide, Prime MM-GBSA were used for improving the accuracy of prediction. Then, Xscore followed by molecular docking was reliable and accurate for forecasting protein-ligand binding free energies (Table I). The docking results were evaluated by comparing values of score energy, SP Glide, XP Glide, and Binding energy. Through analysis of these results of docking simulations, most binding energy scores could accurately forecast the ligand activities. The lowest binding energy and the highest docking score demonstrated that these compounds (ligands) presented well favorable interactions.

The docked ligands **4a**, **5a**, pyrazolo[4,3-c]pyridine derivatives showed the best range of Docking score, XP Gscore and Binding energy (Table I).

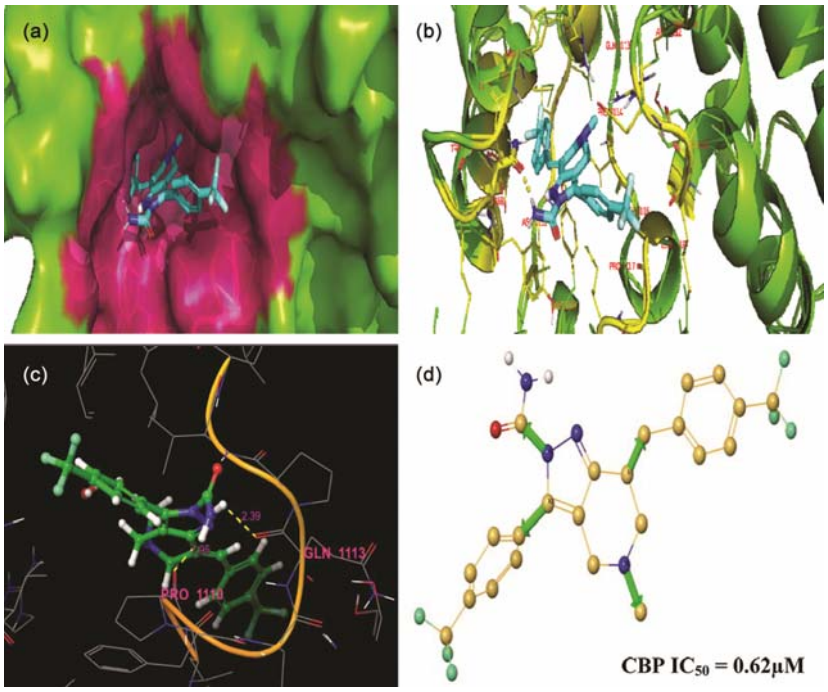


Figure 2 — Schematic representation of **4a** in the binding pocket 1abd. The co-crystal structure of D and the CBP bromodomain (1.38 Å resolution; PDB code 5KTU)

Table II — Interactions with Amino Acids for the Synthesized Compound against CREBBP bromodomain

Compd	Hydrogen Bonding	Hydrophobic Interaction	Water bridges
4a	Asn1168	Pro1110, Phe1111, Val 1115, Leu1120, Ile 1122, Tyr 1125, Ala 1164, Val 1174	Gly1121,Tyr1167,Arg1169 Asp1105,Arg 1112
5KTU	Asn1168	Leu1109, Phe1111,Ile1122, Val1175 Leu1120, Tyr1167, Val1174, Leu1109	Gln1113,Tyr1125, Arg1112, Pro1110

The molecular docking results are recommended enhancement of the polar interaction Gln1113 side chain of the binding site (Figure 2).

Molecular Dynamics Results

Dynamics has become a useful tool for the prediction of usual motion of the molecular system. It explains protein structure and investigates the stability of the compounds. However, the large conformational space is more stable at lower simulated temperature[28]. The molecular dynamics simulations time scale is 10-00 nsec with the protein and solvent system good[29]. It is a very useful tool in drug discovery to synthesize new targeted drug molecule interaction with ligand and protein molecule[30].The molecular dynamics results are recommended enhancement of the polar interactions with the Asn1168 side chain of the binding site (Table II). In this case acetyl lysine ligand is hydrogen bond donor and acceptor for the amide side chain of the MD simulations with Asn1168, possible interaction (Figure 3).

Protein-Ligand RMSD

The binding mode of the CREBBP by interaction solvent MD simulations of the compound (Figure 4).

If independent 1 µs MD runs are random velocities. The root-mean-square deviation in the time series (RMSD) of compound **4a** shows that the binding mode and stability, although deviations of different magnitude are observed in the two MD runs (Figure 5).

The additional support to docking and binding mode MD simulations is a key role. For the optimization process, the analysis of the interaction motifs along the MD trajectories is efficiently used (Figure 6).

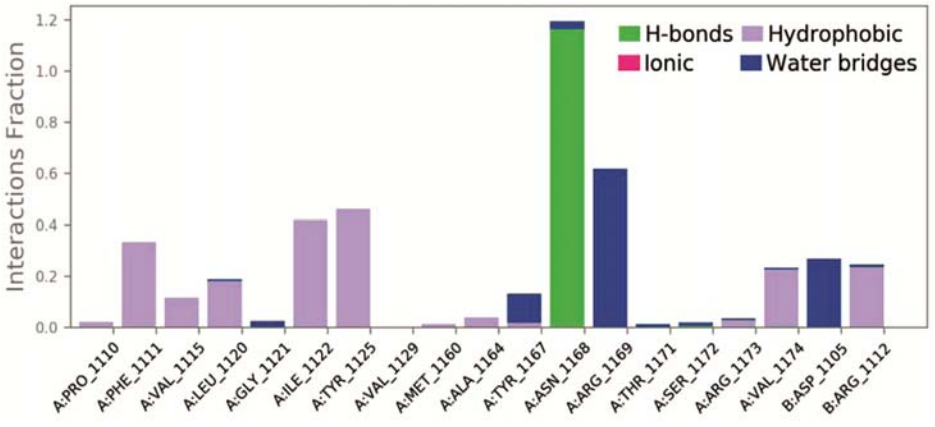


Figure 3 — Lead molecule protein-ligand interaction of compound **4a**

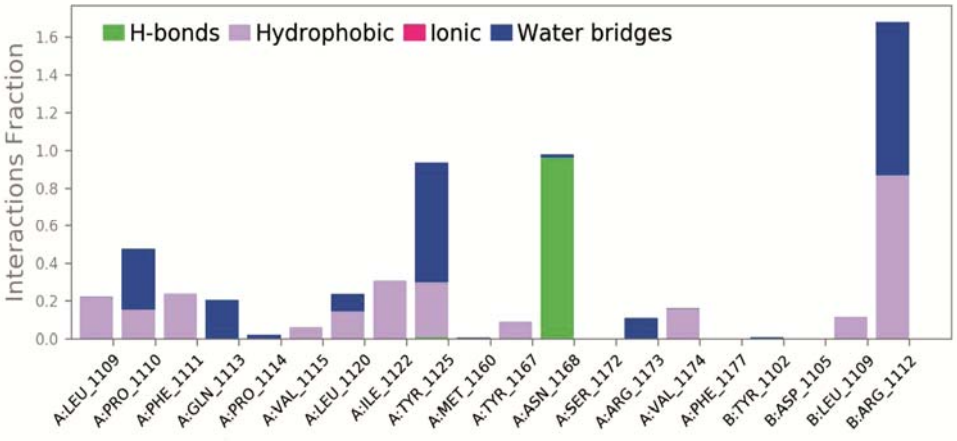


Figure 4 — Co-Crystal 5KTU protein-ligand interaction CREBBP inhibitors

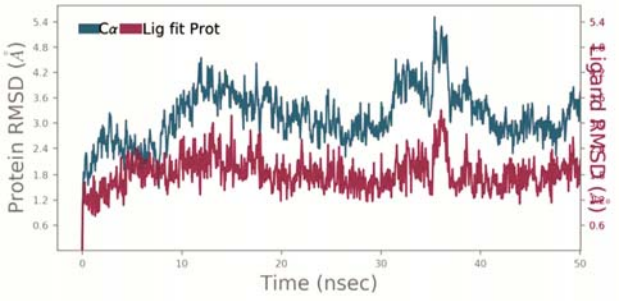


Figure 5 — Structural stability and multiple binding modes of Lead molecule protein-ligand RMSD of compound **4a**

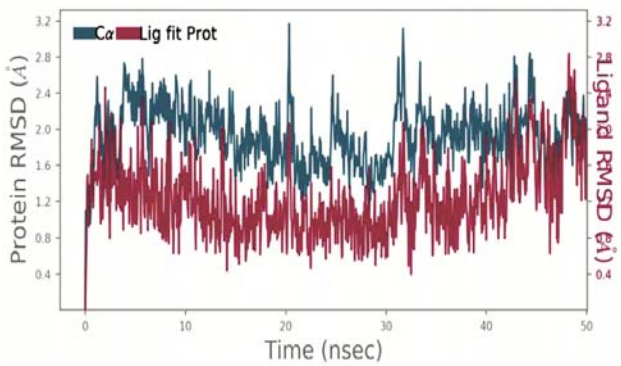


Figure 6 — Structural stability and multiple binding modes of co-crystal protein-ligand RMSD with the CREBBP bromodomain in 50 ns

Biological Studies

The biological studies are used to determine the anti-cancer activity. The human tumor cell lines were derived from nine different cancer types: breast, leukemia, melanoma, lung, colon, central nervous system, ovarian, renal, prostate cancers. Due to its high potency and selectivity, anticancer agents consisting of combined molecules have gained great interests. The *in vitro* anticancer activities against leukemia human cell lines for the synthesized compounds. *In vitro* antitumor assay of the new pyrazolopyridines toward leukemia Moreover, compound 4a IC50 = 62.5µg exhibited interesting

efficacy on all tested compounds. The standard drug taken was Dox for leukemia cancer cell lines (Figure 7, Figure 8).

Experimental Section

Materials and methods

The synthesized compounds were prepared by conventional heating and microwave irradiation technique. The structure of the prepared compounds was confirmed by different spectroscopic tools. All starting materials were purchased from Merck. The chemical structures of the obtained compounds were been confirmed by spectral analyses IR spectra were recorded as KBr pellets on a Perkin-Elmer instrument, ^{1}H and ^{13}C NMR spectra were determined on a 400 MHz spectrometer and chemical shifts are expressed as δ (ppm) against TMS as internal reference. Mass spectra were recorded on 70 eV. Column chromatography was performed on Merck silica gel 60 (particle size 0.06 mm-0.20 mm). The purity of the compounds was checked by thin-layer chromatography performed with Merck silica gel 60 F254 aluminium sheets. Spots were detected by their absorption under UV light. All compounds prepared in this paper are new and their structures confirmed from spectral data.

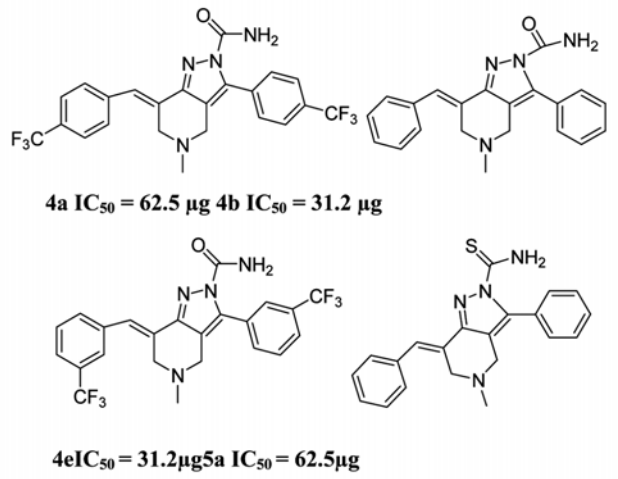


Figure 7 — Pyrazolopyridine cores tested and found potential against U937 Cell line Leukemia inhibition

Computational Studies

Preparation of Ligands

Structures of ligands sketched and saved in SDF format were imported *via* selecting files. The imported ligands **4a-g**, **5a** were set to minimize under force field OPLS3e. Minimization calculations can be performed on all structures of pyrazolo[4,3-c]pyridine derivatives.

Preparation of Protein

X-ray crystalline structure of protein 5KTU was imported from Protein Data Bank (PDB) to workspace, which further set to preprocess followed by review and modification to remove unwanted chains and residues, further refined under forcefield of OPLS3e. The results were monitored in the job monitor.

Molecular Docking

The compounds selected for molecular docking have some collective structural features. All the lead compounds showed good binding energy and exhibited interactions and better lower free energy values, indicating more thermodynamically favored interaction. As for Glide docking, crystal structures of

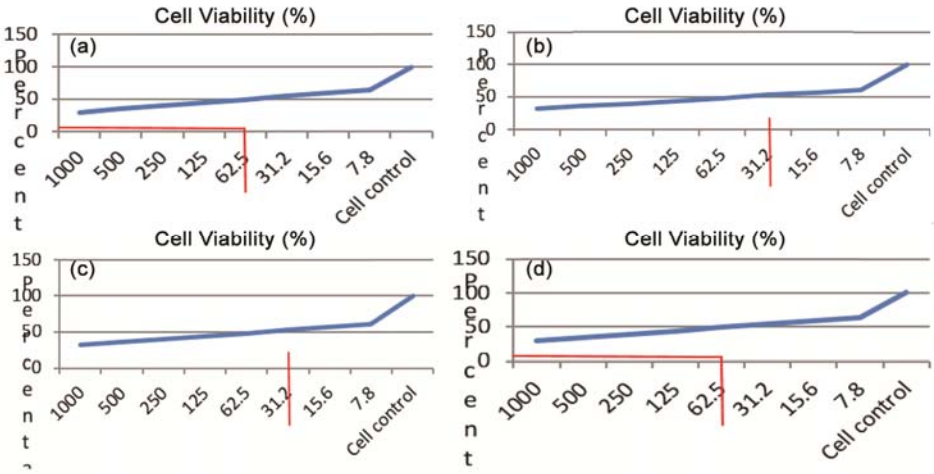


Figure 8

5KTU have been prepared by the protein preparation wizard in Schrödinger suite. Afterwards, receptor grids were generated before docking with the active site determined by the position of co crystal ligand. Crystal structures of 5KTU were imported into Glide, defined as the receptor structure and the location of active sites with a box. The PSLS3e force field was used for grid generation. The standard precision (SP) and the extra precision (XP) protocols were set for docking studies with crucial residues, in constrained binding to get accurate results. Binding affinity was retrieved running Prime MM-GBSA. All other parameters were maintained as default

Molecular dynamics

All computational works were performed using Schrödinger suite (Small-Molecule Drug Discovery Suite 2018-2, Schrödinger, LLC, New York, NY, 2018).

Biological testing

In vitro evaluation of the anticancer activity

Primary anticancer assays were performed according to the NCI protocol as described elsewhere. The compounds were added at a single concentration and the cell cultures were incubated for 24h.The results for each compound are reported as the percent growth (GP %) of treated cells when compared to untreated control cells. The range of percent growth shows the lowest and the highest percent growth found among the cancer cell lines.

Cell line and culture

U937 cell line was obtained from NCCS, Pune. The cells were maintained in Minimal Essential Medium supplemented with 10% FBS, penicillin (100 U/mL), and streptomycin (100 µg/mL) in a humidified atmosphere of 50 µg/mL CO_2 at 37°C.

In vitro assay for anticancer activity (MTT assay) (Mosmann, 1983)

Cells (1 × 105/well) were plated in 24-well plates and incubated in 37°C with 5% CO_2 condition. After the cell reaches the confluence, the various concentrations of the samples were added and incubated for 24hrs.100µl/well (5mg/mL) of 0.5% 3-(4, 5-dimethyl-2-thiazolyl)-2, 5-diphenyl--tetrazolium bromide (MTT) was added and incubated for 4 hours. After incubation, 1 mL of DMSO was added in all the wells.The absorbance at 570nm was measured with UV- Spectrophotometer using DMSO as the blank. Measurements were performed and the concentration required for a 50% inhibition (IC50) was determined graphically (Table III). The % cell viability was calculated using the following formula:

Table III — $IC_{50}$of the tested compounds on leukemia cancer

Compd	IC50 (µg /mL)
4a	62.5
4b	31.2
4e	31.2
5b	62.5
Standard-DOX	15.6

% cell viability = A570 of treated cells / A570 of control cells × 100

Graphs are plotted using the % of Cell Viability at Y-axis and concentration of the sample in X-axis. Cell control and sample control is included in each assay to compare the full cell viability assessments.

(E)-7-(4-(Trifluoromethyl)benzylidene)-3-(4-trifluoro methyl)phenyl)-4,5,6,7-tetrahydro-5-methyl pyrazole [4,3-c]pyridine-2-carboxamide, 4a

Equal moles of chalcone, semicarbazide were treated with 10% sodium hydroxide solution and refluxed for 6hr at 80°C mixture (3E,5E)- 3,5-(trifluoromethyl)dibenzylidene -1-methylpiperidin-4-one was treated with semicarbazide with 10% sodium hydroxide were refluxed at 80ºC in a heating mantel for 6hrs produced. Yield 74%. m.p.159°C. IR: 3550 NH_2, 3155 aromatic stretching, 1675 C=O, 1600 C=C, 980 cm^{-1} C-F; ^{1}H NMR: δ 2.09 (s,3H,CH_3), 6.12(s,2H,NH_2), 7.24(m,Ar-H), 8.2 (s,1H, NH); ^{13}C NMR: δ 12.3,40.6, 60.9, 110.4,126.4, 130.7, 135.2, 138.2, 147.7, 161.8; ESI-MS: *m/z* 480.

(E)-7-Benzylidene-4,5,6,7-tetrahydro-5-methyl-3-phenyl pyrazole[4,3-c]pyridine-2-carboxamide, 4b

Yield: 88%. m.p.115-117ºC. IR: 1640 –CN,3300 –NH_2, 1555 C=C, 1690 C=O, Aromatic stretching 2925 cm^{-1}; ^{1}H NMR: δ 2.27 (s,3H,CH_3), 7.18-7.26 (m,Aromatic H), 7.65 (NH); ^{13}C NMR: δ 12.2, 40.3, 95.4, 116.4, 126.4, 128.7, 135.2, 135.2, 138.2, 164.6; ESI-MS: *m/z* 344.

(E)-7-(4-Diethylamino)benzylidene)-3-(4-diethy lamino) phenyl-4,5,6,7-tetrahydro-5-methyl pyra zole[4,3-c]pyridine-2-carboxamide, 4c

Yield:84%. m.p.137°C. IR: 3458 NH_2, 3165 aromatic stretching, 1685 C=O,1600 cm^{-1} C=C; ^{1}H NMR: δ 2.07 (s,3H,CH_3), 3.05 (s,6H,N(CH_3)2), 6.12 (s,2H,NH_2), 7.24 (m,Ar-H), 8.9 (s,1H, NH); ^{13}C NMR: δ 12.6, 29.7, 44.1, 45.6, 66.7, 110.5, 111.8, 122.5, 128.0, 130.7, 132.2, 147.3, 190.0; ESI-MS: *m/z* 486.

(7E)-4,5,6,7-Tetrahydro-5-methyl-7-(E)-3-phenyl allylidene)-3-styryl pyrazolo[4,3-c]pyridine-2-carboxamide, 4d

Yield:72%. m.p.168°C. IR:3450 NH_2, 3125 aromatic stretching, 1685 C=O, 1610 cm^{-1} C=C; ^{1}H NMR: δ 2.15 (s,3H, CH_3), 6.18 (s, 2H, NH_2), 7.14 (m, Ar-H), 8.7 (s, 1H, NH); ^{13}C NMR: δ 12.2 , 40.7, 60.7, 110.2, 126.4, 130.7, 135.2, 137.2, 160.8; ESI-MS: *m/z* 396.

(E)-7-(3-(Trifluoromethyl)benzylidene)-3-(3-trifluoromethyl)phenyl)-4,5,6,7-tetrahydro-5-methyl pyrazole[4,3-c]pyridine-2-carboxamide, 4e

Yield:78%. m.p.159°C. IR: 3550 NH_2, 3155 aromatic stretching, 1675 C=O, 1600 C=C, 980 cm^{-1} C-F. ^{1}H NMR: δ 2.09 (s, 3H, CH_3), 6.12 (s, 2H, NH_2), 7.12 (m, Ar-H), 8.2 (s, 1H, NH); ^{13}C NMR: δ 12.3, 40.6, 60.9, 110.4, 126.4, 130.7, 135.2, 138.2, 147.7, 161.8; ESI-MS: *m/z*480.

(E)-7-(2,4-Dimethylbenzylidene)-4,5,6,7-tetrahydro-methyl-3-(2,4 dimethylphenyl)pyrazolo[4,3-c]pyridine-2-carboxamide, 4f

Yield:74%. m.p.143°C. IR: 3430 NH_2, 3115 aromatic stretching, 1675 C=O,1600 cm^{-1} C=C; ^{1}H NMR: δ 2.06 (s, 3H, CH_3), 6.12 (s, 2H, NH_2), 7.14 (m, Ar-H), 8.2 (s, 1H, NH); ^{13}C NMR: δ 12.5, 40.5 , 60.5, 76.8, 110.4, 126.4, 130.7, 135.2, 138.2, 150.5, 168.8; ESI-MS: *m/z* 400.

(E)-7-(4-Methoxybenzylidene)-4,5,6,7-tetra hydro-3-(4-methoxyphenyl)-5-methylpyrazole[4,3-c]pyridine-2-carboxamide, 4g

Yield:74%. m.p.143°C. IR: 3560 NH_2, 3135 aromatic stretching, 1665 C=O, 1600 cm^{-1} C=C; ^{1}H NMR: δ 2.01 (s, 3H, CH_3), 6.12 (s, 2H, NH_2), 7.34 (m, Ar-H), 8.4 (s, 1H, NH); ^{13}C NMR: δ 12.5, 40.5, 60.5, 76.8, 110.4, 126.4, 130.7, 135.2, 138.2,150.5, 163.8; ESI-MS: *m/z* 404.

(E)-7-Benzylidene-4,5,6,7-tetrahydro-5-methyl-3-phenyl pyrazole[4,3-c]pyridine-2-carbothioamide, 5a

Equal moles of mixture (3E,5E)- 3,5-dibenzylidene -1-methylpiperidin-4-one are treated with thiosemicarbazide with 10% sodium hydroxide were refluxed at 80°C in a heating mantle for 6hrs produced 5a. Yield: 88%. m.p.115-117°C. IR: 1640 –CN,3300 –NH_2, 1555 C=C, 2300 C=S, Aromatic stretching 2925 cm^{-1}; ^{1}H NMR: δ 2.05 (s, 3H, CH_3), 6.9 (S, α CH), 7.5 (d, β CH), 7.25-7.46 (m, Aromatic H), 8.0 (NH); ^{13}C NMR: δ 12.2, 40.3, 95.4, 116.4, 126.4, 128.7, 135.2, 135.2, 138.2, 176.6; ESI-MS: *m/z* 360.

Conclusion

Here we have outlined the identification of an inhibitor of the CBP/EP300 bromodomains that are potent biochemically and in cells and displays suitable metabolic stability for application as an *in vivo* probe. Compounds are belonging to this class of compounds exhibited moderate to potent anticancer activities in cell line tests. The synthesized compounds were prepared by conventional heating and microwave irradiation technique. Moreover, compound **4a** exhibited interesting efficacy on all tested cell lines, whereas compound **4e** showed good activity on MCF-7 cells. **4a** compounds are eco-friendly, safer and cheaper for the treatment of cancer. The intention of this study is focused to examine the comparative molecular docking studies on the target CREB-binding protein which are responsible for cancer with the ligand of **4a-5j**. The comparative docking studies were done by "Schrödinger Maestro 12.1". **4a** has a better binding score (−6.237 Kcal/mol) than the other standard drugs. The ligand **4e** with the Glide score –5.572, shows the binding affinity with the amino acid (AA) residues GLU1113, PRO1110. These residues are acting as a conclusive pocket for the potential ligand. Hence it has been concluded that **4a** as a potent inhibitor for CREB-binding protein in cancer.

Supplementary Information

Supplementary information is available in the website http://nopr.niscair.res.in/handle/123456789/60.

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