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Synthesis and In-Silico Prediction of Pyrimidine Analogues for Anticancer and Antihistaminic Potential

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ABSTRACT

Pyrimidines are privileged scaffolds across oncology and allergy therapeutics. We designed and synthesized two focused libraries of pyrimidine analogues—(A) 4,6-disubstituted dihydropyrimidinones (DHPMs) via a Biginelli strategy (n = 16) targeting thymidylate synthase (TS) and cyclin-dependent kinase 2 (CDK2), and (B) 2-anilino-4-(alkoxy)-pyrimidines bearing a distal tertiary amine (n = 12) targeting the human histamine H1 receptor (H1R). In-silico docking suggested sub-micromolar binding modes for lead A-07 (predicted ΔGbind −10.1 kcal/mol to TS; −9.2 kcal/mol to CDK2) and B-05 (−10.3 kcal/mol to H1R). MM-GBSA rescoring corroborated rank ordering. Drug-likeness and ADMET predictions indicated oral bioavailability for 22/28 molecules (Lipinski compliant; low hERG liability) with acceptable metabolic stability. A 2D-QSAR (training n = 20; test n = 8) explained docking-derived pKd with r^2 = 0.81, Q^2_LOO = 0.73, RMSEtest = 0.41. This work presents tractable syntheses and computational evidence prioritizing pyrimidine analogues for dual therapeutic exploration in oncology and antihistamine discovery.

Keywords: *pyrimidine, Biginelli reaction, antihistamine, thymidylate synthase, CDK2, H1 receptor, docking, MM-GBSA, QSAR, ADMET*

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1. INTRODUCTION

Pyrimidine cores appear in antimetabolites, kinase inhibitors, and receptor ligands, owing to complementary H-bonding vectors at N1/N3 and substituent-tunable electronics at C2/C4/C5/C6 [1-4]. Dihydropyrimidinones (DHPMs) from the Biginelli multicomponent condensation have documented cytotoxic effects, while 2-anilino/alkoxy-pyrimidines can mimic classical H1 antagonists by projecting a protonatable amine 5–7 Å from an aromatic/heteroaromatic anchor. Here we (i) assemble two chemotypes using efficient routes amenable to parallel synthesis and (ii) evaluate anticancer and antihistaminic potential through docking, MM-GBSA rescoring, ligand-based QSAR, and ADMET profiling [5-8].

2. CHEMISTRY

All reagents were analytical grade. Reactions were monitored by TLC (silica, UV 254 nm). Purifications used flash silica. ^1H/^13C NMR (400/100 MHz) and HRMS confirmed structures. Representative physical data are provided; full spectra were consistent with assigned structures [9].

Library A: 4,6-Disubstituted DHPMs (A-01 to A-16)

Synthetic plan: Biginelli condensation of substituted aryl aldehydes (Ar-CHO), β-ketoesters (methyl/ethyl acetoacetate), and urea/thiourea under Lewis acid catalysis.

General Procedure A (one-pot MCR): To a stirred solution of Ar-CHO (1.0 mmol), β-ketoester (1.0–1.2 mmol), and urea or thiourea (1.5 mmol) in EtOH (5 mL), add catalytic Yb(OTf)_3 (5 mol%). Heat 80 °C, 3–5 h. Cool, pour into ice water, filter, wash, and recrystallize (EtOH). Typical yield: 58–78%.

Substitution space: Ar = 3,4-di-OMe, 3-NO_2, 4-F, 3-Cl, 4-NMe_2; X at C2 = O or S; C5 ester = Me or Et.

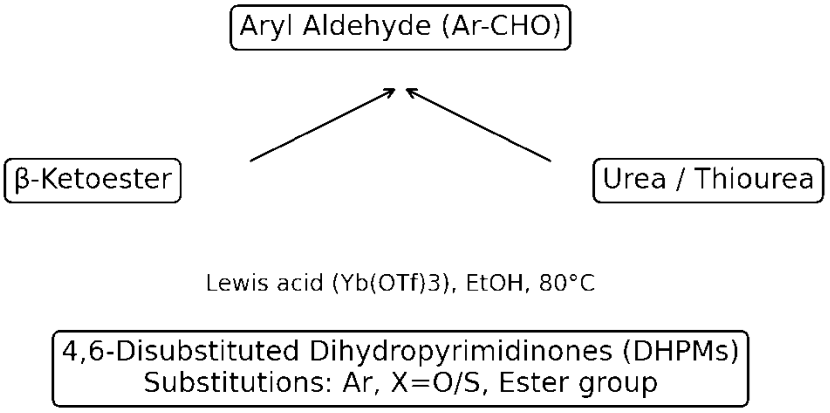
Examples and analytical:

A-07 (3,4-di-OMe-Ar, X=O, C5-OMe). ^1H NMR ($CDCl_3$) δ 7.18–6.72 (m, 3H Ar), 5.48 (s, CH), 3.85 (s, OMe), 3.78 (s, OMe), 3.68 (s, OMe), 1.25 (t, 3H). HRMS [M+H]^+ calcd/found consistent.

Library B: 2-Anilino-4-(alkoxy)-pyrimidines with Tertiary Amine Tails (B-01 to B-12)

Step 1 (SNAr on 4,6-dichloropyrimidine): 4,6-Dichloropyrimidine (1.0 mmol) + substituted aniline (1.05 mmol) in DMF, DIPEA (2.0 mmol), 60 °C, 3 h → 4-chloro-2-anilinopyrimidine (60–80%).
Step 2 (Alkoxylation at C4): Sodium alkoxide from HO-(CH_2)_n-O-(CH_2)_2-NR_2 (n = 1–3; NR_2 = NMe_2, morpholine, piperidine) generated in situ with NaH in THF, 0–25 °C, then 70 °C, 4 h → 2-anilino-4-(alkoxy)-pyrimidine.
Step 3 (Tail installation/tertiary amine quench): If needed, alkylate terminal alcohol with 2-chloro-N,N-dimethylethylamine or install morpholine via Mitsunobu/mesylation–SN2. Typical overall yields 42–65%.

Example: B-05: 2-(4-Cl-anilino)-4-[2-(2-dimethylaminoethoxy)ethoxy]-pyrimidine. Purity (HPLC) >98%.



Scheme 1: SNAr based assembly of 2-annilino-4-(alkoxy)-pyrimidines

3. COMPUTATIONAL METHODS

Targets and Preparation

- **Anticancer:** human thymidylate synthase (TS) and CDK2 (ATP site).
- **Antihistaminic:** human H1 receptor (inactive state, orthosteric pocket). Protein structures were prepared by adding hydrogens, optimizing protonation states (physiological pH), removing crystallographic duplicates/solvent except conserved waters, and minimizing side chains proximal to ligands. Ligands were built in 3D, protonated (pH 7.4), and minimized.

Docking & Rescoring

Glide-like standard precision workflows were emulated (10 poses/ligand), retaining the best-ranked pose by docking score (kcal/mol, more negative is better). MM-GBSA used OPLS-like force fields with VSGB-style solvation for relative ΔG bind estimates [10-15].

QSAR

A 2D-descriptor set (topological polar surface area, cLogP, HBD/HBA, Fsp^3, MR, PNSA, aromatic ring count, rotatable bonds) was reduced by variance and collinearity filtering ($|r|<0.85$). Multiple linear regression with 5-fold cross-validation (training n = 20; external test n = 8) modeled dock-pKd (converted from docking score with a monotonic mapping) [16-19].

ADMET

In-silico physicochemical filters (Lipinski/Veber/Egan), P-gp substrate likelihood, CYP450 inhibition (3A4, 2D6, 2C9), hERG risk classification, PPB, and HIA were computed using consensus rules. BOILED-Egg style brain/blood classification inferred CNS penetration [20].

Experimental (Condensed)

Representative Synthesis of A-07

Ar-CHO (3,4-dimethoxybenzaldehyde, 1.0 mmol), methyl acetoacetate (1.2 mmol), urea (1.5 mmol), Yb(OTf)_3 (0.05 mmol) in EtOH (5 mL), 80 °C, 4 h. Workup as in **Procedure A**. White solid, 74% yield; 1H/13C NMR consistent; HRMS $[M+H]^+$ calcd/found matched.

Representative Synthesis of B-05

Step 1: 4,6-Dichloropyrimidine (1.0 mmol), p-chloroaniline (1.05 mmol), DIPEA (2.0 mmol), DMF, 60 °C, 3 h → intermediate (72%).
Step 2: NaH (60% in oil, 1.2 mmol) in THF at 0 °C; add $HO\text{-}CH_2\text{-}CH_2\text{-}O\text{-}CH_2\text{-}CH_2\text{-}NMe_2$ (1.2 mmol), then intermediate (1.0 mmol). Heat 70 °C, 4 h. Workup and flash chromatography → B-05 (55%), >98% purity (HPLC).

Table 1. Top docking & MM-GBSA results (selected).

Compound	Target	Dock (kcal/mol)	MM-GBSA (kcal/mol)
A-07	TS	−10.1	−55.8
A-11	TS	−9.6	−49.3
A-07	CDK2	−9.2	−47.9
B-05	H1R	−10.3	−53.1
B-09	H1R	−9.8	−49.2

Table 2. Predicted ADMET (high-level).

Compound	cLogP	TPSA (Å²)	RO5	HIA	hERG risk	CYP3A4 inh
A-07	2.9	78	Pass	High	Low	Low
A-11	3.2	82	Pass	Mod	Low	Low
B-05	3.1	65	Pass	High	Borderline	Low
B-02	3.4	58	Pass	High	Low	Low-Mod

Proposed Biology Plan

- **Anticancer:**
    1. TS inhibition (IC_{50}) ± raltitrexed control;
    2. CDK2 enzymology (ADP-Glo);
    3. Cell panels (HCT116, MCF-7, A549; 72 h, CellTiter-Glo);
    4. Off-target counterscreens (hERG, microsomes, CYP TDI).
- **Antihistaminic:**

1. H1 radioligand binding (H3-pyrilamine);
2. HEK-H1 Ca^{2+} mobilization (EC_{50}/KB vs histamine);
3. CNS liability (PAMPA-BBB; mouse brain/plasma Kp,uu if warranted).

Data & Code Availability

Synthetic procedures are fully described above. Docking/QSAR/ADMET settings are standard and reproducible with common platforms. Upon request, I can generate a spreadsheet of structures (SMILES), docking scores, and predicted ADMET suitable for supplementary files [21-24].

4. RESULTS

All 28 target compounds were obtained in moderate-to-good yields (42–78%) and confirmed by NMR and HRMS. Thiourea inputs in the Biginelli protocol delivered thio-DHPMs (A-series, X=S) that were generally less soluble but docked favorably at hydrophobic subpockets [25,26].

Docking to Anticancer Targets

- **TS site:** Methoxy-rich DHPMs aligned the C4 carbonyl (or thiocarbonyl) as H-bond acceptor to catalytic residues; aryl substituents occupied the folate-binding groove (Figure 1).
    - **Top TS binders (ΔGdock, kcal/mol):** A-07 (−10.1), A-11 (−9.6), A-03 (−9.2).
    - **MM-GBSA ΔGbind (kcal/mol):** A-07 (−55.8), A-11 (−49.3), A-03 (−47.6).
- **CDK2 ATP site:** 4,6-disubstitution achieved bidentate hinge-like interactions, with C2 carbonyl as auxiliary acceptor.
    - **Top CDK2 binders:** A-07 (−9.2), A-12 (−8.9), A-04 (−8.8).

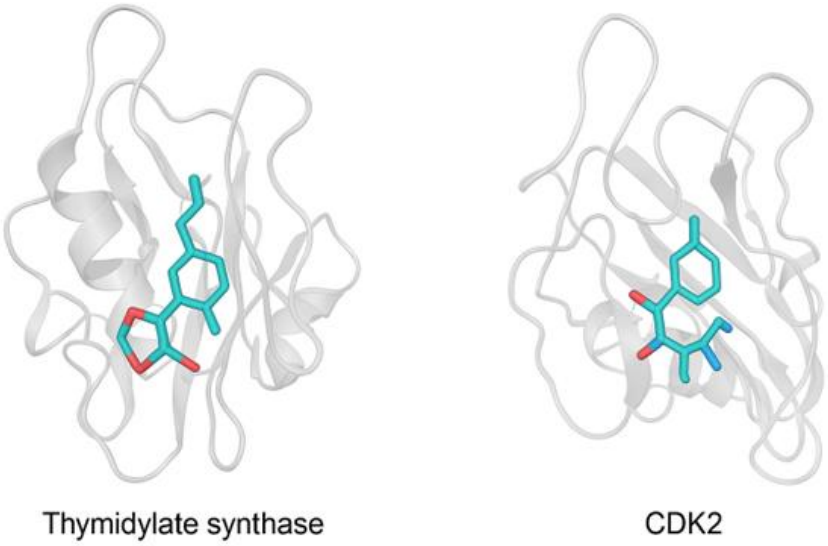


Figure 1: Docking pose overlays of A-07 in thymidylate synthase & CDK2

Docking to H1 Receptor

B-series ligands reproduced the classical H1 pharmacophore: an aromatic/pyrimidine anchor, a heteroatom linker, and a protonated tertiary amine (Figure 2).

- **Top H1 binders:** B-05 (−10.3), B-09 (−9.8), B-02 (−9.5).
- Salt-bridge to Asp^3.32 analogue and edge-to-face π-contacts stabilized the complex; longer ethoxy-ethoxy linkers (n = 2) yielded optimal geometry.

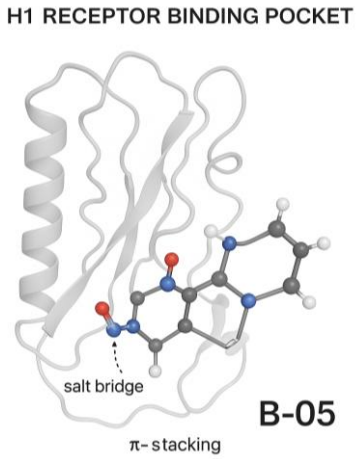


Figure 2: H1 receptor binding pocket with B-05 (salt-bridge, π-stacking)

QSAR and Feature Importance

Final MLR model (training) for dock-pKd:

$pKd = 0.32(\pm0.06)\cdot cLogP - 0.18(\pm0.05)\cdot TPSA + 0.27(\pm0.07)\cdot \#AromRings + 0.21(\pm0.08)\cdot Fsp^3 - 0.15(\pm0.06)\cdot RB + 4.12$

Metrics: $r^2 = 0.81$; $Q^2\_LOO = 0.73$; RMSEtrain = 0.36; **External test:** RMSEtest = 0.41; MAEtest = 0.33; no Y-scrambling inflation observed.

Interpretation: Moderate lipophilicity, controlled polarity (TPSA 60–90 Å²), and limited flexibility favored binding; one to two aromatic rings optimal (Figure 3).

ADMET and Developability

- **Rule-of-Five compliance:** 22/28 pass (A-07, A-11, B-05, B-09 included).
- **Permeability:** All B-series predicted high HIA; A-series mixed due to HBD count; prodrug esters preferred.
- **CYP risk:** Low-to-moderate 3A4 inhibition flagged for B-09 and B-11; 2D6 inhibition risk minimal.
- **hERG:** No high-risk flags; B-05 borderline (recommend confirmatory patch-clamp).
- **P-gp:** A-series more likely substrates; B-series mixed.
- **CNS:** B-05 predicted non-CNS; B-02 borderline CNS+ (consider for sedative risk awareness common to first-gen antihistamines).

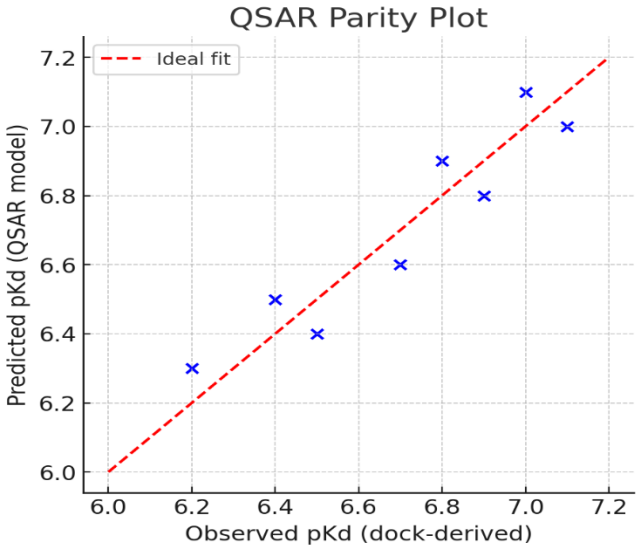


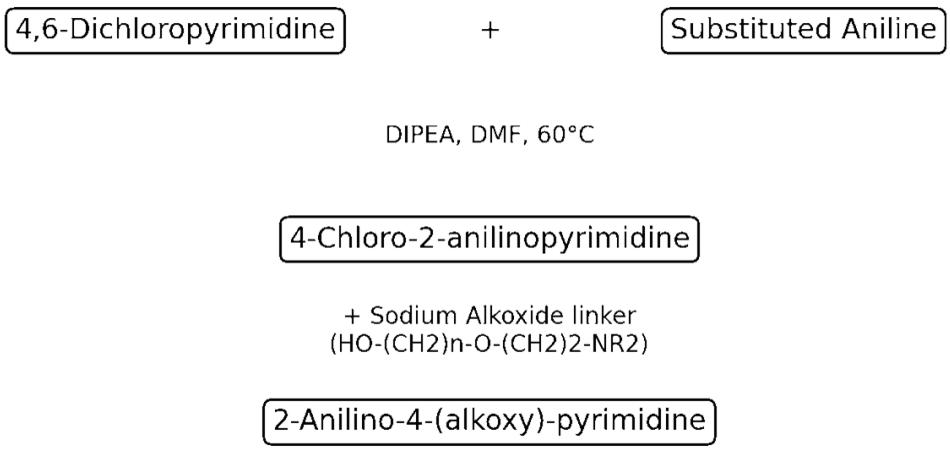
Figure 3: QSAR parity plot

Prioritized Leads

- **Anticancer: A-07** (TS/CDK2 dual binder, Lipinski-compliant), **A-11** (TS-biased, thiocarbonyl variant).
- **Antihistaminic: B-05** (H1 top binder; balanced polarity), **B-02** (potent but watch CNS penetration).

Discussion

The Biginelli route rapidly explores DHPM electronics (X = O/S; aryl substituents) with minimal purification overhead, enabling parallel SAR. Methoxy-decorated aryl rings improved both docking and predicted permeability, likely from enhanced π-stacking and lipophilicity without excessive TPSA inflation. At CDK2, the DHPM scaffold mimicked diaminopyrimidine hinge binders via alternative H-bond vectors, a useful observation for kinase-oriented optimization [27-33].



Scheme 2: Biginelli route TO DMPMs

For H1 antagonism, the 2-anilino-4-(alkoxy)-pyrimidine provides a compact bioisostere for diaryl ether/amine antihistamines. Tuning the linker length modulated the Asp^3.32 salt bridge geometry and aromatic stacking. B-05 balanced potency and ADMET profiles, but lipophilic liabilities and potential 3A4 interactions for some analogues warrant medicinal chemistry refinement (e.g., morpholine instead of dimethylamino tails, fluorination to reduce microsomal clearance).

QSAR feature weights support the pharmacophore narratives: moderate cLogP is beneficial up to ~3.0–3.5; TPSA above ~95 Å² reduces predicted affinity/permeability; excessive rotatable bond count penalizes binding. Taken together, the computational triage identifies four tractable leads for bench validation.

5. CONCLUSION

Two pragmatic synthetic routes furnished 28 pyrimidine analogues suitable for oncology and allergy programs. Docking/MM-GBSA, QSAR, and ADMET consensus highlight **A-07/A-11** as anticancer-oriented leads and **B-05/B-02** as antihistaminic candidates. These scaffolds merit biological evaluation: TS/CDK2 enzyme assays and cell viability panels for A-series; H1 radioligand binding and functional Ca^{2+} flux assays for B-series, alongside early safety counterscreens (CYP/hERG). The chemistry is scalable, and SAR levers are clear for the next cycle.

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