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RESEARCH ARTICLE

Design, Synthesis, Biological Evaluation, and *In Silico* ADMET Studies of 1,8-Naphthyridine Derivatives as an H1-receptor Inhibitor

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ABSTRACT

In the present study, 1,8-naphthyridine-3-carboxylic acid derivatives (5a1, 5a2, 5b1, and 5b2) were designed, synthesized, and screened for their *in vitro* H1-antihistaminic activity. H1R inhibitory activity of the synthesized derivatives was calculated by the modified Van Arman technique, histamine-induced bronchoconstriction in guinea pigs. A good bronchorelaxant effect of compounds was observed in histamine-contracted guinea pig tracheal chain through H1-receptor antagonism. In addition, the hypothetically resulted compounds are checked for their reliability on other *in silico* drug designing online web services like SwissADME predictor. *In silico* ADMET analysis results show that all the derivatives had negligible toxicity, good absorption, and solubility profile. These compounds may serve as possible lead for establishing safe and effective antihistaminic agent(s).

Keywords: 1,8-Naphthyridine, ADMET, antihistaminic activity, SwissADME

INTRODUCTION

One of the most important chemical mediators in the body is histamine and through its interaction with H1 receptors, present in most tissues, is involved in the pathophysiology of allergic rhinoconjunctivitis, urticaria, and asthma.[1] The first-generation antihistamines are effective and relatively inexpensive against these symptoms; though they also cause sedation and dry mouth at therapeutic doses, due to their blood–brain barrier (BBB) penetration and lack of receptor specificity.[2] In contrast, most of the second-generation H1 antagonists such as terfenadine, cetirizine, and astemizole[3] have greatly gained benefit-to-risk ratio compared to their predecessors. These drugs are lesser perspective to cross the BBB and possess the higher receptor specificity[4] and they are labeled as "non-sedative antihistamines." The second-generation drugs also consist of various structural characteristics similar to well-established first-generation antihistamines. Azelastine is an antiallergic agent which demonstrates histamine H1-receptor antagonist activity and also inhibits histamine release from mast cells following antigen and non-antigen stimuli.[5]

From exhaustive literature survey of 1,8-naphthyridine, it has been found to be a potent antiallergic agent; in addition, derivatives of 1,8-naphthyridine are reported to have a broad range of biological activities such as antiallergic,[6] antilipolytic,[7] A1 adenosine antagonistic,[8] anti-inflammatory,[9,10] and PDE inhibiting[11] activities. It is evident from literature that azelastine contains three pharmacophore groups: (1) Phthalazinone, (2) p-chlorobenzyl, and (3) a basic moiety N-methylazepine which are responsible for its potent antiallergic properties. In view of this and the fact that naphthyridine moiety is isosteric with phthalazinone nucleus of azelastine, it has been thought worthwhile to synthesize 1,4-dihydro-4-oxo,1,8-naphthyridine-3-carboxylic acid derivatives having 4-chlorobenzyl and benzyl substitution at 1 position and basic moiety attached to the naphthyridine nucleus through a carbonyl group. The basic moiety to be substituted will include phenylpiperazine, toluidine, etc., which are already present in some well-known antihistaminic agents. Thus, it is sincerely expected that the resulting compound is likely to possess antihistaminic activity. In the present work, we report the synthesis and antihistaminic activity of 1,8-naphthyridine-3-carboxylic acid derivatives by

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modifying aromatic ring terminal 3-carboxylic acid end [Figure 1].

An effective drug molecule should not only have optimum efficiency and safety against the therapeutic target but also show adequate ADMET profiling at optimum therapeutic dose. In the past few years, a large number of *in silico* models being developed for analysis of ADMET profile and pharmacokinetic characteristics.[12] At present, the term pan-assay interference compounds has emerged to describe apparent bioactive molecules that are able to interfere in readouts through interaction with unrelated biological targets and/or testing methods.[13]

MATERIALS AND METHODS

General

All experiments were carried out under air atmosphere unless confirmed otherwise. Reagents and solvents were usually the best quality commercial-grade products and were used without further purification. The synthesis of the target compound of 1,8-naphthyridine-3-carboxamide derivatives was achieved by the route depicted in the scheme [Figure 2].[8,10,14]

Melting points were checked using open capillary method. The structures were chemically analyzed by Fourier transform infrared (FTIR), proton nuclear magnetic resonance (^{1}H NMR), elemental analysis, and mass spectrum data. The IR spectra of synthesized compounds were recorded on Shimadzu FTIR spectrophotometer. ^{1}H NMR spectra were recorded through Bruker (Bruker BioSpin AG, Fällanden, Switzerland) Avance III 400 MHz system spectrometer using dimethyl sulfoxide (DMSO) as a solvent. The chemical shifts were measured at units (reported as ppm) relative to TMS and the spin multiplicities were given as s (singlet), d (doublet), t (triplet), and m (multiplet). MS and high-resolution mass spectra were obtained using Electrospray Ionization (ESI) technique on a Bruker's Fourier transform ion cyclotron resonance mass spectrometer. All the reactions were routinely monitored by TLC analysis on silica gel GF254 purchased from HiMedia using methanol:chloroform (1:4) as a solvent system.

Chemistry

Synthesis of diethyl 2-((pyridine-2-ylamino) methylene) malonate (1)

2-Aminopyridine (1 mmol) and diethyl ethoxy methylene malonate (1 mmol) were heated at 120–130°C for 2 h, the resulting ethanol was evaporated and crude malonate was obtained; this crude malonate was purified by recrystallized from light petroleum ether. Yield: 90%, mp 72–74°C, ^{1}H NMR: (DMSO); δ 1.29 (t, 6H, methyl), 4.20 (q, 4H, methylene), 7.14 (t, 1H, H1 Ar), 7.67 (d, 1H, H2Ar), 7.79 (t, 1H, H4Ar), 9.06 (d, 1H, NH), 11.18 (d, 1H, CH). IR: (KBr cm^{-1}); 3271.27 (N-

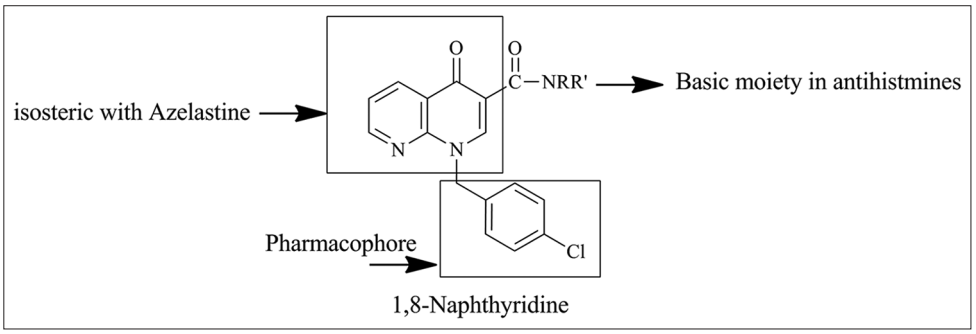

Figure 1: Design of molecules

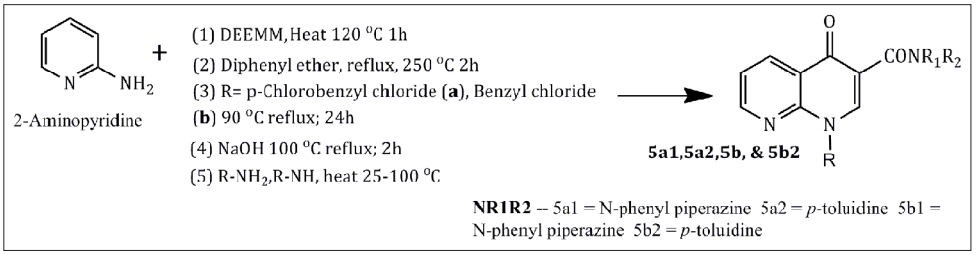

Figure 2: Scheme

H), 1649.14 (N-H bend), 1311.59 (C-N), 3057.17 (C-H), 2931.80, 2897.08 (C-H), 1649.14(C=C), 923.90 (C-H), 1693.64, (CO ester) 1147 (C-O ester). MS: (m/z); 264.11 (M^+), Chemical Formula: $C_{13}H_{16}N_2O_4$, MWt 264.28, Analysis: C, 59.08; H, 6.10; N, 10.60.

Synthesis of ethyl 4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylate (2)

Crude ester (1) (0.017 mol) diphenyl ether in access at 240–250°C for 1 h, the resultant solution was cool at room temperature and washed with petroleum ether. The white powder was collected and recrystallized from dimethylformamide. Yield: 81%, mp 187–188°C, ^{1}H NMR: (DMSO); δ 1.32 (t, 3H, methyl), 4.21 (q, 2H, methylene), 7.53 (d, 1H, H7 Ar), 7.82 (d, 1H, H5 Ar), 8.50 (d, 1H, H6 Ar), 8.47 (s, 1H, H2), 4 (s, 1H NH). IR:(KBr cm^{-1}); 3398.2 (N-H), 3070.8 (C-H) 1739.5 (CO ester), 1672.8 (CO Ar ring) and 1571.8, 1490.6 (C=N and C=C), 791 and 776.6. MS: (m/z); 218.07 (M^+), Chemical Formula: $C_{11}H_{10}N_2O_3$, MWt 218.21, Analysis: C, 60.55; H, 4.62; N, 12.84.

Synthesis of ethyl 1-(4-chlorobenzyl)-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylate (3a) and ethyl 1-benzyl-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylate (3b)

NaH (0.0870 g, 1.81 mmol, 50% in mineral oil) was added to a solution of 7-methyl-1,8-naphthyridine 2 (0.350 g, 1.5 mmol) in 10 mL of dry DMF. After 1 hr, 4-chlorobenzyl chloride (for 3a) and benzyl chloride (for 3b) (1 mmol) were added and the reaction mixture was stirred for 24 h at room temperature and solution was evaporated *in vacuo* and the addition of ethyl ether caused the precipitation of the title compound as a pure solid.

Ethyl 1-(4-chlorobenzyl)-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylate (3a)

Yield: 80%, mp 182–184°C^{1}H NMR: (DMSO); δ 8.77 (d, 1H), 8.71 (d, 1H), 8.71 (s, 1H), 7.41 (d, 1H), 7.31 (d, 1H), 7.26 (d, 1H), 5.60 (s, 2H), 4.38 (q, 2H), 1.40 (t, 3H). IR:(KBr cm^{-1}); 3242.34, 3120.82 (aliphatic), 3070.58 (aromatic), 1663.50, 1625.99 (keto), 1090 (C-Cl). Mass: m/z 342 (M^+), Chemical Formula: $C_{18}H_{15}ClN_2O_3$, MWt 356.80, Analysis: C, 63.10; H, 4.41; N, 8.12.

Ethyl 1-benzyl-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylate (3b)

Yield: 81%, mp 154–155°C,^{1}H NMR: (DMSO); δ 8.79 (d, 1H Ar), 8.73 (d, 1HAr), 8.72 (s, 1H), 7.41 (d, 1HAr), 7.32 (m, 5H Ar), 5.65 (s, 2H methylene), 4.39 (q, 2H), 1.40 (t, 3H). IR: (KBr cm^{-1}); 3000–3100 (aromatic) 1725, 1691 (CO keto), cm^{-1}; MS: (m/z); 308 (M^+), Chemical Formula: $C_{18}H_{16}N_2O_3$, MWt 322.36, Analysis: C, 70.12; N, 5.21; N, 9.04.

Synthesis of 1-(4-chlorobenzyl)-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid (4a) and 1-benzyl-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid(4b)

The appropriate ethyl ester 3a and 3b (4.13 mmol) were refluxed for 2 h in a mixture of aqueous 10% sodium hydroxide (5 mL) and ethyl alcohol (5 mL). After cooling, the solution was adjusted to pH 4 with aqueous 10% hydrochloric acid. The resulting precipitate was collected by filtration, washed with H_2O, and recrystallized.

1-(4-Chlorobenzyl)-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid (4a)

Yield: 75%, mp 235–237°C, 1H NMR: (DMSO); δ 9.34 (s, 1H, H2), 7.72(d, 1H, H5 Ar), 6.74 (t, 1H, H6 Ar), 7.32(m, 4H, Ar), 4.87 (s, 2H, CH2 methylene), 11.00 (s 1H Acid). IR: (KBr cm^{-1}); 3069.1, 2998.7 (C-H aromatic), 1714.0 (CO acid), 1692.1 (C=O) ring), 1090.7 (C-Cl). MS: (m/z); 314.05(M^+), Chemical Formula: $C_{16}H_{11}ClN_2O_3$, MWt 314.72, Analysis: C, 69.00; H, 4.45; N, 9.50.

1-Benzyl-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid(4b) (4b)

Yield: 71%, mp >300°C,^{1}H NMR: (DMSO); δ 11.0 (s,1H, COOH), 8.21 (d, 1H, H7Ar), 6.71 (d,1H, H6Ar), 7.62(d, 1H, H5Ar), 7.13 (m, 5H, Ar), 4.81 (s, 2H CH2 methylene), 9.10 (s. 1H, CH-Ph), IR: (KBr cm^{-1}): 3069.1, 2998.7 (C-H aromatic), 1714.0 (CO acid), 1692.1 (CO Ar ring). MS: (m/z); 280 (M^+), Chemical Formula: $C_{16}H_{12}N_2O_3$, MWt 280.28, Analysis: C, 68.56; H, 4.32; N, 9.99.

Synthesis of 1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid derivatives (5a1, 5a2, 5b1, and 5b2)

A mixture of the 1,8-naphthyridine-3-carboxylic acids 4a and 4b (1 mmol) and appropriate amine (10 mmol) were heated in a sealed tube at 27–100°C for 24 h. After cooling, the reaction mixture was

treated with diethyl ether to give titled compound as a pure white solid.

1-(4-Chlorobenzyl)-3-(4-phenylpiperazine-1-carbonyl)-1,8-naphthyridin-4(1H)-one (5a1)

Yield: 55.5%, mp 181–183°C,^{1}H NMR: (DMSO); δ 2.40 (s, 3H, methyl), 9.07 (s, 1H, H2), 8.55 (d, 1H, Ar), 7.48 (d, 1H, Ar), 5.80 (s, 2H, CH2 Ar), 7.24-7.33 (m, 5H, Ar) 2.57 (t, 4H, piperazine), 3.46 (t, 4H, piperazine), IR: (KBr cm^{-1}), 3069.1, 2998.7 (C-H), 1714.0 (CO keto), 1692.1 (CO ring), 1081(C-Cl). MS: (m/z); 458 (M^+), Chemical Formula: $C_{26}H_{23}ClN_4O_2$, MWt 458.94, Analysis: C, 67.04; H, 5.05; N, 12.21.

1-(4-Chlorobenzyl)-4-oxo-N-(p-tolyl)-1,4-dihydro-1,8-naphthyridine-3-carboxamide (5a2)

Yield: 75%, mp 147–149°C, ^{1}H NMR: (DMSO); δ 2.24 (s, 3H CH3 methyl), 5.34 (s, 2H, CH2Ar), 8.51 (s, 1H, NH), 6.98–7.12 (m, 3H, Ar), 7.02 (d,1H, Ar), 7.16 (d, 2H, Ar), 7.36 (d, 2H, Ar), 7.44 (d, 2H, Ar), 7.80 (d, 1H,Ar), 8.38 (d, 1H, Ar), IR: (KBr cm^{-1}); 3069.1, 2998.7 (C-H), 1714.0 (CO keto), 1692.1 (CO Ar ring), 1081(C-Cl). MS: (m/z); 403 (M^+), Chemical Formula $C_{23}H_{18}ClN_3O_2$, MWt 403.86, Analysis: C, 68.40; H, 4.49; N, 10.40.

1-benzyl-3-(4-phenylpiperazine-1-carbonyl)-1,8-naphthyridin-4(1H)-one (5b1)

Yield: 76%, mp 147–149°C, ^{1}H NMR: (DMSO); δ 9.87 (d, 1H, NH), 8.94 (s, 1H, H2), 8.53 (d, 1H, H5 Ar), 7.46 (d, 1H, H6 Ar), 7.18 (m, 2H, Ar), 6.90-6.71 (m, 3H, Ar), 4.70 (s, 2H, CH2 methylene), 3.03 (m, 4H, piperazine), 2.73 (m, 2H, CH2), 2.60 (m, 4H, piperazine), 1.85–1.08 (m, 10H, cyclohexyl). IR: (KBr cm^{-1}); 3069.1, 2998.7 (C-H), 1714.0 (CO keto), 1692.1 (CO Ar ring), 1081(C-Cl). MS: (m/z); 424 (M^+), Chemical Formula: $C_{26}H_{24}N_4O_2$, MWt 424.49, Analysis: C, 71.01; H, 7.45; N, 14.79.

1-Benzyl-4-oxo-N-(p-tolyl)-1,4-dihydro-1,8-naphthyridine-3-carboxamide (5b2)

Yield: 74%, mp 147–149°C, ^{1}H NMR: (DMSO); δ 9.24 (s, 1H, H2), 2.21 (s, 3H, methyl), 8.52 (d,1H, Ar), 7.56 (d, 1H, Ar), 7.96 (d, 1H, Ar), 7.23 (m, 5H, Ar), 5.81 (s, 2H, Ar), 9.90 (d, 1H,NH), 7.23–7.79 (m, 4H, Ar), IR: (KBr cm^{-1}); 3069.1, 2998.7 (C-H), 1714.0 (CO keto), 1692.1 (CO Ar ring), 1081(C-Cl). MS: (m/z); 269 (M^+), Chemical Formula: $C_{23}H_{19}N_3O_2$, MWt 369.42, Analysis: C, 74.78; H, 5.18; N, 11.37.

Pharmacology

The synthesized derivatives were screened for *in vivo* H1R inhibitory activity and sedative-hypnotic activities. The animals were placed in single colony cages at 25 ± 2°C, RH of 45–55%, under a 12:12 h light and dark cycle; animals were fed nutritionally balanced and adequate standard feed. All the animals were acclimatized for minimum 1 week period before being used for experimental purposes. The institutional animal ethics committee allowed the protocol for this animal study.

Antihistaminic activity

A modified Van Arman technique was selected for determining the antihistaminic activity for the synthesized derivatives.[15] Male Dunkin Hartley Guinea pigs of weight about 300–350 g fasted for 12 h were used taking six animals for the individual group. The test compounds (5a1–5b2) were given by oral route at a dose of 10 mg/kg in 1% carboxymethyl cellulose (CMC) suspension and challenged with histamine aerosol (0.2% aqueous solution of histamine hydrochloride 3 mL) in a vaponephrine pocket nebulizer sprayed into a closed transparent cage. The respiratory status resulting in the form of increasing the degree of bronchoconstriction was noted. The time for onset of convulsions (preconvulsion) was noticed. Animals remaining stable for >6 min were measured as completely protected against histamine-induced bronchospasm. Intraperitoneal injection of chlorpheniramine maleate at xg was given toward recovery of test animals. The mean preconvulsion time of animals, treated with the test compounds, was compared against control and is expressed in terms of percentage protection [Table 1].

% Protection = $(1^-(T1/T2))\times100$

Where, T1 - A preconvulsive time of control and T2 - A preconvulsive time of test compound.

Sedative-hypnotic activity

The sedative-hypnotic activity of test compounds was determined by measuring the decrease in

locomotor activity using actophotometer.[16-22] Swiss albino mice of about 20–25 g were selected as test animals keeping six mice in each group. Basal activity score was taken, and then, tested compounds 5a1, 5a2, 5b1, and 5b2 and the standard drug (chlorpheniramine maleate) were given orally at the dose of 5 mg/kg in 1% CMC suspension. Activity scores were recorded at 1, 2, and 3 h after drug administration. Percent decrease in locomotor activity was calculated in terms of percentage reduction in motor activity and results shown in Table 1.

% Reduction in motor activity = ((A- B)/A) x 100

Where, A - basal score and B - score after drug treatment.

Statistical analysis

A statistical study on the biological activities of the test compounds was performed by one-way ANOVA followed by Dunnett's test (manually). In all cases, a significance level of each group was calculated and compared against the control. A value $P < 0.5$ denoted statistical significance in all cases.

ADME prediction

The SwissADME wave server evaluated the pharmacokinetics parameter, druglikeness, and medicinal chemistry friendliness for small molecules. The molecular properties such as molecular weight <500 g/mol, <5 numbers of hydrogen bond donors, <10 numbers of hydrogen bond acceptors, and <10 rotatable bonds were chosen as criteria.[23] For *in silico* toxicity prediction eMolTox (http://xundrug.cn/moltox.), a publicly available web server which predicts different kinds of toxic endpoints from toxicology related *in vitro*/*in vivo* experimental data and analyzes the toxic substructures.[24]

RESULTS AND DISCUSSION

Chemistry

The intermediate ethyl 4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylate (2) was prepared by refluxing malonate (1) in diphenyl ether. The carboxylate, ethyl 1-(4-chlorobenzyl)-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylate (3a), and ethyl 1-benzyl-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylate (3b) were prepared by refluxing 1,8-naphthyridine-3-carboxylate (2) and p-chlorobenzyl chloride and benzyl chloride, respectively. Acid hydrolysis of 1,8-naphthyridine-3-carboxylate (3a and 3b) gives 1-substituted1,8-naphthyridine-3-carboxylic acids (4a and 4b). The title compounds were synthesized by heating the appropriate amine and 1-substituted1, 8-naphthyridine-3-carboxylic acids (4a and 4b) in a sealed tube. The title compounds 5a1, 5a2, 5b1, and 5b2 were obtained in fair to good yields.

As per the spectral data of compound, FTIR and ^{1}H NMR showed the presence of characteristic peak at 1650–1692 and 3300 cm^{-1} (for CO and -NH stretching), 3100–3000 cm^{-1} (phenyl group), and 1380 cm^{-1} (for ether linkage) and δ around 9.87, 7.18, 4.70, 3.03, 2.60, and 1.85–1.08 ppm due to existence of aromatic. -NH, aromatic. -CH, piperazinyl, and cyclohexyl. In case of compounds 3–5 as per the ^{1}H NMR spectroscopy, spectral data at 8.70 and 8.90 ppm indicated the presence of p-chlorobenzyl and benzyl moiety. Further, the structures were established by mass spectral data in accordance with their molecular formula.

Antihistaminic activity

The compounds were found to have considerable antihistaminic activity [Table 1]. Percentage

Table 1: Antihistaminic and sedative-hypnotic activity of compounds 5a1, 5a2, and 5b1-5b2

Percent CNS depression					
Compound code	**Time of onset of convulsion (s)**	**% Protection**	**1 h**	**2 h**	**3 h**
5a1	359±4.65	62.81±0.317	6.68±0.19	7.32±0.13	4.60±0.16
5a2	355±4.23	61.75±0.265	8.28±0.10	9.42±0.17	5.09±0.10
5b1	349±5.35	57.33±1.35	10.1±1.77	11.1±1.73	7.1±1.85
5b2	338±5.38	51.27±1.82	11.13±1.66	12.1±1.05	9.1±1.48
Control	116±4.56	–	6.10±0.49	4.1±0.59	4±0.91
Chlorpheniramine	394±4.43*	70.09±0.33*	38.80±32**	34.80±0.72**	29.58±0.72**

Each value represents the mean±SEM (n=6). Significance levels *P<0.001, **P>0.05. CNS: Central nervous system

protection results showed that test compounds show significant percentage protection. Synthesized compounds were effective with the significant percentage of protection score and they are comparable to that of standard drug. Biological studies indicated that different substituent over the first position of the 1,8-naphthyridine ring exerted varying antihistaminic activity. The presence of the chlorine atom (compounds 5a1 and 5a2) showed better activity than the unsubstituted compound (compounds 5b1 and 5b2). Placement of alicyclic amines with the additional heteroatom (phenyl piperazinyl compound 5a1) led to a further increase in activity.

Sedative-hypnotic activity

Sedation is one of the main side effects of H1-receptor inhibitors, the test compounds were also screened for their *in vivo* sedative-hypnotic activity. This activity was evaluated by measuring the decrease in locomotor activity. The data of this study revealed that almost all the test compounds had mild activity (<13%). Hence, these compounds can be developed as therapeutically useful non-sedative antihistamines [Table 1].

ADMET prediction

The toxicological property from chemical structures of the compounds was predicted using SwissADME server and the compounds were found non-mutagenic and safer. BBB score was found significant for tested compounds and comparable to that of control. SwissADME measures the log *P* value (partition coefficient) which is a well-established assessment for the hydrophilicity of compounds [Table 2]. Higher log *P* value results in lower hydrophilicity and, thus, lower absorption, and penetration. The log S value serves as solubility; the lower the log S value, the greater the solubility which would improve the absorption of the drug candidate.[25] The higher TPSA score is interrelated with lower membrane penetration and compounds with increased TPSA were better substrates for p-glycoprotein. Thus, comparing the derivatives, poor TPSA score was favorable for the druggable property. It was also analyzed that a compound with better CNS permeation should have lower TPSA score.[26,27]

Table 2: Physicochemical descriptors and ADME parameters of compounds 5a1, 5a2, and 5b1-5b2

Molecule	Rotatable bonds	H-bond acceptors	H-bond donors	TPSA	Log P	Log S	GI absorption	BBB permeation	log Kp (cm/s)	Lipinski violations	Bioavailability score	PAINS alerts	Synthetic accessibility
5a1	5	3	0	58.44	3.65	−5.58	High	Yes	−6.02	0	0.55	0	3
5a2	5	3	1	63.99	4.03	−5.4	High	Yes	−5.58	0	0.55	0	2.66
5b1	5	3	0	58.44	3.16	−4.99	High	Yes	−6.25	0	0.55	0	2.96
5b2	5	3	1	63.99	3.44	−4.81	High	Yes	−5.81	0	0.55	0	2.62
Chlorphenamine	5	2	0	16.13	3.48	−3.82	High	Yes	−5.57	0	0.55	0	2.7
Azelastine	3	3	0	38.13	4.15	−5.2	High	Yes	−5.53	1	0.55	0	3.62

TPSA: Topological polar surface area, Log P: Lipophilicity, Log S: Water solubility, Log Kp: Permeability coefficient, PAINS: Pan-assay interference structure

Table 3: *In silico* predicted toxic properties (eMolTox) of compounds 5a1, 5a2, and 5b1-5b2

Action	Injury	5a1		5a2		5b1		5b2		Chlorphenamine		Azelastine	
		Outcome	Confidence	Outcome	Confidence	Outcome	Confidence	Outcome	Confidence	Outcome	Confidence	Outcome	Confidence
Agonist of the AP-1 signaling pathway	Cancer	INC	0	INC	0	INC	0	INC	0	INC	0	+Ve	0.992
Carcinogenic potency (Mouse)	Carcinogenicity	INC	0	INC	0	INC	0	INC	0	INC	0	INC	0
Modulator of neuronal acetylcholine receptor; alpha3/beta4	Central nervous system	−Ve	0.982	−Ve	0.987	−Ve	0.999	−Ve	0.99	−Ve	0.987	−Ve	0.992
Modulator of acetylcholinesterase	Central nervous system	−Ve	0.988	−Ve	0.995	−Ve	0.987	−Ve	0.995	−Ve	0.997	INC	0
Modulator of serotonin transporter	Central nervous system, blood, heart, gastrointestinal	−Ve	0.996	−Ve	1	−Ve	0.998	−Ve	1	+Ve	0.997	−Ve	0.995
Modulator of dopamine D2 receptor	Central nervous system, gastrointestinal, heart, kidney	−Ve	0.996	−Ve	0.999	−Ve	0.996	−Ve	1	−Ve	0.998	INC	0
Modulator of dopamine D1 receptor	Central nervous system, kidney, heart	−Ve	1	−Ve	0.995	−Ve	0.996	−Ve	0.999	−Ve	0.983	−Ve	0.982
Modulator of serotonin 3a (5-HT3a) receptor	Gastrointestinal, Heart, central nervous system	−Ve	0.98	−Ve	0.989	INC	0	−Ve	0.997	INC	0	INC	0
Modulator of histamine H2 receptor	Gastrointestinal, immune, heart	−Ve	0.994	INC	0	−Ve	0.993	INC	0	INC	0	INC	0
Induce genotoxicity in human embryonic kidney cells	Genotoxicity	INC	0	INC	0	INC	0	INC	0	INC	0	INC	0
Modulator of HERG	Heart	INC	0	INC	0	INC	0	INC	0	INC	0	+Ve	0.999
Modulator of bradykinin B2 receptor	Heart, respiratory, kidney, central nervous system	−Ve	0.993	−Ve	0.997	−Ve	0.991	−Ve	0.994	−Ve	0.987	−Ve	0.992
Modulator of TNF-alpha	Immune	INC	0	INC	0	INC	0	INC	0	−Ve	0.985	−Ve	0.986
Modulator of CB2 receptor	Immune, nervous system	−Ve	0.989	INC	0	−Ve	0.993	INC	0	−Ve	0.999	INC	0
Modulator of H1 receptor	Immune, nervous system, heart, gastrointestinal	−Ve	0.998	−Ve	0.999	−Ve	0.997	−Ve	1	+Ve	0.984	+Ve	0.999
Modulator of HMG-CoA reductase	Kidney	−Ve	0.998	−Ve	0.987	−Ve	0.982	−Ve	0.986	−Ve	0.983	−Ve	0.993
Activators of cytochrome P450 2A9	Liver	−Ve	0.985	INC	0	INC	0	INC	0	INC	0	−Ve	0.983
Lungs tox (acute oral, LD50 <500 mg/kg)	Lung	INC	0	INC	0	INC	0	INC	0	INC	0	INC	0
Acute oral toxicity (mouse, LD50 <5 mg/kg)	Mouse	INC	0	INC	0	INC	0	INC	0	−Ve	0.996	−Ve	0.996
Modulator of MAO A	Pharmacokinetics, central nervous system	−Ve	0.999	INC	0	−Ve	0.993	INC	0	INC	0	−Ve	0.992
Acute oral toxicity (rat, LD50 <5 mg/kg)	Rat	INC	0	INC	0	INC	0	INC	0	INC	0	INC	0
Skin sensitization	Skin	−Ve	0.994	−Ve	0.991	−Ve	0.993	−Ve	0.995	INC	0	−Ve	0.99

INC: Inconclusive, −Ve: Negative, +Ve: Positive

Synthetic accessibility (SA) is a key issue to consider in the selection process. Obviously, for a reasonable number of drug molecules, medicinal chemists are the best able to determine SA. The SA score of the entire synthesized compound was found comparable with the reference drug [Table 2]. The lipophilicity of all tested compounds is in a range defined by the rule of five (log $P < 5$), thus providing a good prognosis for intestinal permeability. The eMolTox predict toxicity of a given molecule is likely to have. From 174 data sets for toxicity prediction about 20 dataset results of prediction as shown in Table 3. All the ADMET parameters were found to be favorable for the compounds 5a1, 5a2, 5b1, and 5b2 and even better in some sense than that of a reference drug.

CONCLUSION

The 1,8-naphthyridine-3-carboxylic acid derivatives were synthesized, characterized, and then screened for antihistaminic activity. The 1,8-naphthyridine derivatives have promising antihistaminic activity against histamine-induced bronchospasm on conscious guinea pigs model. The sedative-hypnotic activity of derivatives was found to be negligible when compared to chlorpheniramine maleate; therefore, they could be a lead molecule for further modification to obtain a therapeutically useful antihistaminic agent. The *in silico* ADME profile, toxicity, druglikeness, and SA result together with *in vivo* antihistaminic activities make compounds 5a1, 5a2, 5b1, and 5b2 promising leads for the development of selective and potent antihistaminic agents.

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CONFLICTS OF INTEREST

The authors disclose that there are no conflicts of interest.

REFERENCES

1. Simons FE, Simons KJ. The pharmacology and use of H1-receptor-antagonist drugs. N Engl J Med 1994;330:1663-70.
2. Ellis EF, Adkinson NF, Yungingen JW, Busso WW. H1-Receptor Antagonists. New York: Musby-Year Book, Inc.; 1985. p. 856-91.
3. Chairungsrilerd N, Furukawa K, Ohta T, Nozoe S, Ohizumi Y. Pharmacological properties of alpha-mangostin, a novel histamine H1 receptor antagonist. Eur J Pharmacol 1996;314:351-6.
4. Hopp RJ, Bewtra A, Nair NM, Townley RG. The effect of age on methacholine response. J Allergy Clin Immunol 1985;76:609-13.
5. McTavish D, Sorkin EM. Azelastine. A review of its pharmacodynamic and pharmacokinetic properties, and therapeutic potential. Drugs 1989;38:778-800.
6. Sherlock MH, Kaminski JJ, Tom WC, Lee JF, Wong SC, Kreutner W, *et al.* Antiallergy agents 1. Substituted 1, 8-naphthyridin-2(1H)-ones as inhibitors of SRS-A release. J Med Chem 1988;31:2108-21.
7. Aljamal JA, Badawneh M. Antilipolytic effects of 1,8-naphthyridine derivatives β-adrenoceptor antagonists in rat white adipocytes. Chem Biol Drug Des 2017;90:119-27.
8. Ferrarini PL, Betti L, Cavallini T, Giannaccini G, Lucacchini A, Manera C, *et al.* Study on affinity profile toward native human and bovine adenosine receptors of a series of 1,8-naphthyridine derivatives. J Med Chem 2004;47:3019-31.
9. Dianzani C, Collino M, Gallicchio M, Di Braccio M, Roma G, Fantozzi R, *et al*. Effects of anti-inflammatory [1, 2, 4]triazolo[4, 3-a] [1, 8]naphthyridine derivatives on human stimulated PMN and endothelial cells: An *in vitro* study. J Inflamm (Lond) 2006;3:4.
10. Ferrarini PL, Calderone V, Cavallini T, Manera C, Saccomanni G, Pani L, *et al.* Synthesis and biological evaluation of 1,8-naphthyridin-4(1H)-on-3-carboxamide derivatives as new ligands of cannabinoid receptors. Bioorg Med Chem 2004;12:1921-33.
11. Shimamoto T, Inoue H, Hayashi Y. 1-Cycloalkyl-1,8-Naphthyridine-4-One Derivative as Type iv Phosphodiesterase Inhibitor. US Patent 6331548; 2001.
12. Guan L, Yang H, Cai Y, Sun L, Di P, Li W, *et al.* ADMET-score-a comprehensive scoring function for evaluation of chemical drug-likeness. Med Chem Commun 2018. Doi: org/10.1039/C8MD00472B.
13. Baell J, Walters MA. Chemistry: Chemical con artists foil drug discovery. Nature 2014;513:481-3.
14. Lv K, Liu ML, Feng LS, Sun LY, Sun YX, Wei ZQ, *et al.* Synthesis and antibacterial activity of naphthyridone derivatives containing mono/difluoro-methyloxime pyrrolidine scaffolds. Eur J Med Chem 2012;47: 619-25.
15. Van Arman CG, Miller LM, O'Malley MP. SC-10049: A catecholamine bronchodilator and hyperglycemic agent. J Pharmacol Exp Ther 1961;133:90-7.
16. Dews PB. The measurement of the influence of drugs on voluntary activity in mice. Br J Pharmacol Chemother 1953;8:46-8.

17. Pal D, Dutta S, Sarkar A. Evaluation of CNS activities of ethanol extract of roots and rhizomes of *Cyperus rotundus* in mice. Acta Pol Pharm 2009;66:535-41.
18. Pal D, Sannigrahi S, Mazumder UK. Analgesic and anticonvulsant effects of saponin isolated from the leaves of *Clerodendrum infortunatum* Linn. In mice. Indian J Exp Biol 2009;47:743-7.
19. Pal D, Pahari SK, Pathak AK. Evaluation of CNS activities of aerial parts of *Jasminum mutiflorum* Andr. Asian J Chem 2007;19:4452-8.
20. Pal D, Nimse SB, Khatun S, Bandyopadhyaya P. CNS activities of the aqueous extract of *Hydrilla verticillata* in mice. Nat Prod Sci 2006;12:44-9.
21. Pal D, Panda C, Sinhababu S, Dutta A, Bhattacharya S. Evaluation of psychopharmacological effects of petroleum ether extract of *Cuscuta reflexa* Roxb. Stem in mice. Acta Pol Pharm 2003;60:481-6.
22. Pal D, Sahoo M, Mishra AK. Analgesic and anticonvulsant effects of saponin isolated from the stems of *Opunntia vulgaris* mill. In mice. Eur Bull Drug Res 2005;13:91-7.
23. Daina A, Michielin O, Zoete V. SwissADME: A free web tool to evaluate pharmacokinetics, drug-likeness and medicinal chemistry friendliness of small molecules. Sci Rep 2017;7:42717.
24. Doak BC, Over B, Giordanetto F, Kihlberg J. Oral druggable space beyond the rule of 5: Insights from drugs and clinical candidates. Chem Biol 2014;21:1115-42.
25. Ji C, Svensson F, Zoufir A, Bender A. EMolTox: Prediction of molecular toxicity with confidence. Bioinformatics 2018;34:2508-9.
26. Veber DF, Johnson SR, Cheng HY, Smith BR, Ward KW, Kopple KD, *et al.* Molecular properties that influence the oral bioavailability of drug candidates. J Med Chem 2002;45:2615-23.
27. Blake JF. Chemoinformatics-predicting the physicochemical properties of 'drug-like' molecules. Curr Opin Biotechnol 2000;11:104-7.