Synthesis of some biologically active 5-benzylidene-2-aryl-5,6-dihydro-4*H*-[1,3]oxazin-6-ones and 4-benzylidene-1-aryl-3,4-dihydropyrimidobenzimidazoles with bridged nitrogen

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Abstract

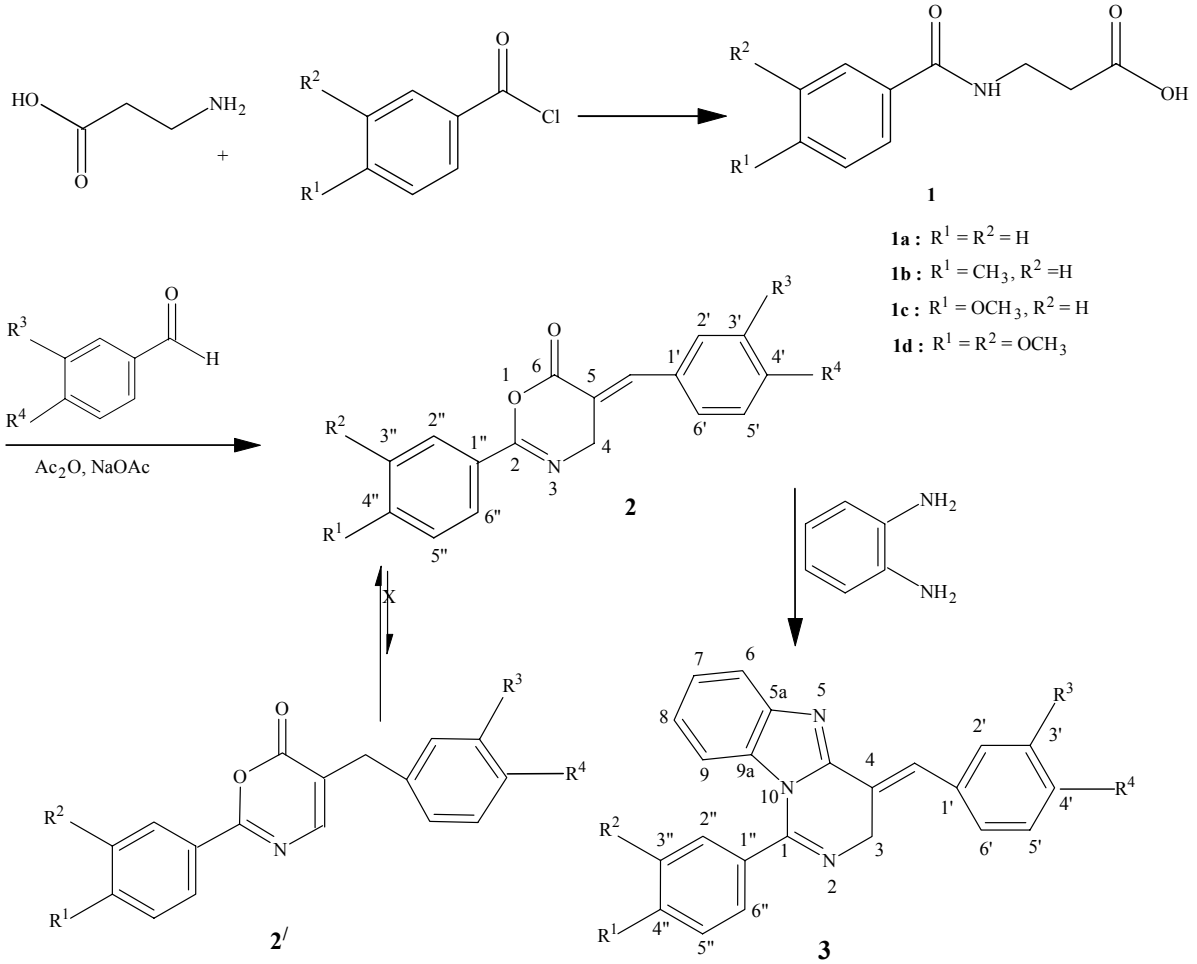
Facile synthesis of differently substituted 5-benzylidene-2-aryl-5,6-dihydro-4*H*-[1,3]oxazin-6-ones **2a-2h** has been achieved by heating a mixture of substituted N-benzoyl-β-aminopropanoic acids **1a-1d** with several aromatic aldehydes in the presence of sodium acetate and acetic anhydride. These compounds **2a-2h,** on refluxing with o-phenylenediamine in dry benzene resulted in the formation of differently substituted 4-benzylidene-1-aryl-3,4-dihydropyrimidobenzimidazoles **3a-3h.** The synthesized compounds **2a-2h** and **3a-3h** were characterized by elemental analysis and spectral studies (IR, ^{1}H NMR and ^{13}CNMR).

Keywords: Erlenmayer δ-azlactone synthesis, 1,3-oxazines and pyrimidobenzimidazoles

Introduction

Benzimidazole derivatives have been found to possess varied pharmacological activities[1-7]. Thiabendazole, a derivative of benzimidazole, stimulated research in various pharmaceutical companies and research institutions. A large number of benzimidazole derivatives were synthesized which have exhibited potent anthelmentic[1], antimicrobial[2-3] (antibacterial, antiviral), anticancer[4-5], anti-fungal[6], pesticidal and herbicidal activities[7]. For example, cambendazole shows a wide range of activity against nematode infection, creeping eruption, enterobiasis, capillariasis and toxocariasis[8]. Mebendazole possesses a broad spectrum of anthelmentic activity[9]. On the other hand, 1,3-oxazine derivatives show interesting reactivity and have been used as chemotherapeutic agents[10]. Tetrahydro-1,3-oxazine derivatives have been used as analgesics, anticonvulsants and antipyretics[11]. Mono and dioxo-1,3-oxazine derivatives related to cyclic urethanes have been used as depressants of the nervous system and sedatives[12]. 4-Oxo-2-thioxo-derivatives have been used as anticonvulsants and sleeping drugs. Dihydro-1,3-oxazines have been suggested as analgesics, sedatives, spasmolytics and fungicides[13-14]. Both tetrahydro- and dihydro- 1,3-oxazine derivatives have been suggested as passive components of azodyes[15].

Pyrimidines and their derivatives are known for their pharmacological properties including antiviral, antibacterial[16-20], antitumor[21] and antihypertensive[20] effects. As a result of their pharmacological, biological, physiological, and medical significance, substituted and condensed pyrimidines form class of compounds of importance and still growing interests. Keeping this in view, it was thought of interest to synthesize certain pyrimidobenzimidazoles with the expectation of their activities supplemented or atleast comparable to those of benzimidazole and pyrimidine derivatives[22]. These compounds have been prepared as per Scheme 1. The mechanisms of formation of **2** and **3** have been shown in Scheme 2 and 3 respectively.



Scheme 1

Results and Discussion

Substituted 3- benzoylaminopropanoic acids **1a-1d** are prepared[23] by the reaction of β–alanine and various benzoyl chlorides in 1:1 molar ratio. As per mechanism shown in Scheme 2, abstraction of hydrogen atom from carboxyl of **1a-1d** by a base ŌAc from anhydrous sodium acetate in presence of acetic anhydride generates a carboxylate ion **4** which attacks on the other carbonyl carbon of the same species intramolecularly resulting in the formation of **5** which on dehydration produces **6**. The abstraction of the hydrogen atom from carbon 5 of compound **6** by ŌAc generates a carbanion on **6** which attacks carbonyl group of substituted aromatic aldehydes producing **7** which simultaneously on elimination of a water molecule lead to the formation of stable differently substituted 5-benzylidene-2-aryl-5,6-dihydro-4*H*-[1,3]oxazin-6-ones **2a-2h**. Further, formation of the products **3a-3h** as per Scheme 3 can be explained by the nucleophilic attack by the amino groups of the o-phenylenediamine on the carbonyl carbon of **2a-2h** compounds to form the intermediates **8**, **9** and **10** in three steps i.e, **(1)**, **(2)** and **(3)** respectively. These intermediates on cyclization followed by the elimination of one water molecule in each case yielded differently substituted 4-benzylidene-1-aryl-3,4-dihydropyrimido[1,6-*a*]benzimidazoles **3a-3h**. Summarily, attempts have been made in the present work to synthesize various differently substituted 5-benzylidene-2-aryl-5,6-dihydro-4*H*-[1,3]oxazin-6-ones **2a-2h** and differently substituted 4-benzylidene-1-aryl-3,4-dihydropyrimido[1,6-a] benzimidazoles **3a-3h**.

Condensation[24-25] of 3-benzoylaminopropanoic acid **1a** and 4-methylbenzaldehyde in 1:1 molar ratio in the presence of anhydrous sodium acetate and acetic anhydride yielded a crystalline compound **2a**. Based on spectral data and elemental analysis, the compound obtained by the condensation of **1a** and 4-methyl benzaldehyde was assigned the structure as 5-(4-methylbenzylidene)-2-phenyl-5,6-dihydro-4*H*-[1,3]oxazin-6-one **2a** ($R^1 = R^2 = R^3 = H$ and $R^4 = CH_3$). In IR spectrum of **2a**, the peaks (υ) at 1685cm^{-1} and 1785cm^{-1} speaking of (-C=N-) and a characterstic δ-azlactone carbonyl respectively; and presence of a sharp singlet at δ 5.85 for the ethylenic proton and a singlet due to two protons at δ 2.95 for the =N-CH_2 protons and a singlet at δ 2.2 due to three benzylic methyl protons in ^{1}HNMR spectrum confirm unambiguously the assigned structure for compound **2a**. The tautomeric shift of proton may generate the corresponding isomeric benzyl analogues **2′** from benzylidene analogues. But in this latter case, the presence of =N-CH_2 gp. chemical shift (δ 2.95) and the shift due to benzylidene proton (-CH= at δ 5.85) would have been lacking. Infact, there ought to have been the presence of a chemical shift of a proton underlined in structure **2′** in Scheme 2 in the down aromatic region and the presence of benzylic protons around (δ 2.3) favouring structures **2′** but this is not the case as both are wanting and hence ruling out the formation of isomeric benzyl analogues **2′** and conforming unambigousoly the structure **2.** Condensation of **1a** with veretraldehyde and other substituted 3-benzoylaminopropanoic acids **1b-1d** with four different aldehydes, two for each of **1b-1d** in 1:1 molar ratio yielded differently substituted 5-benzylidene-2-aryl-5,6-dihydro-4*H*-

[1,3]oxazin-6-ones **2a-2h** respectively in good yields Table 1. The structures of all these compounds were established on the basis of spectral data and elemental analysis.

Table 1. Differently substituted 5-benzylidene-2-phenyl-5,6-dihydro-4*H*-[1,3]oxazin-6-ones 2a-2h with mp's, yields and mol. formulae

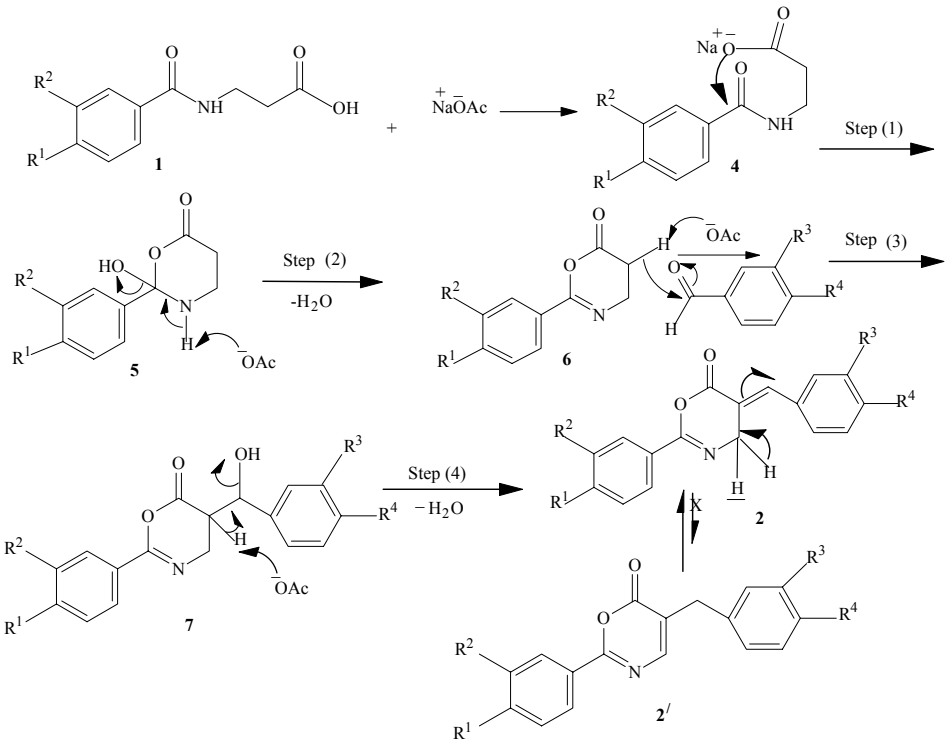
Compound	R	Mp's (ºC)	Yield (%)	Mol. formulae (M^+)	Calcd. formula% Obsd. formula%		
					C	**H**	**N**
2a	$R^1 = R^2 = R^3 = H$, $R^4 = CH_3$	128	68	$C_{18}H_{15}NO_2$	77.97 77.98	5.41 5.42	5.05 5.01
2b	$R^1 = CH_3$, $R^2 = R^3 = H$, $R^4 = OCH_3$	138	67	$C_{19}H_{17}NO_3$	74.26 74.01	5.53 5.51	4.56 4.59
2c	$R^1 = OCH_3$, $R^2 = R^3 = R^4 = H$	123	67	$C_{18}H_{15}NO_3$	73.72 73.52	5.11 5.15	4.77 4.82
2d	$R^1 = R^2 = OCH_3$, $R^3 = H$, $R^4 = CH_3$	135	69	$C_{20}H_{19}NO_4$	71.21 71.17	5.63 5.72	4.15 4.17
2e	$R^1 = R^2 = H$, $R_3 = R^4 = OCH_3$	132	69	$C_{19}H_{17}NO_4$	70.58 70.52	5.26 5.32	4.33 4.35
2f	$R^1 = CH_3$, $R^2 = H$, $R^3 = R^4 = OCH_3$	138	72	$C_{20}H_{19}NO_4$	71.21 71.09	5.63 5.65	4.15 4.20
2g	$R^1 = OCH_3$, $R^2 = R_3 = H$, $R^4 = CH_3$	126	68	$C_{19}H_{17}NO_3$	74.26 74.22	5.53 5.55	4.56 4.58
2h	$R^1 = R^2 = OCH_3$, $R^3 = R^4 = H$	139	70	$C_{19}H_{17}NO_4$	70.58 70.55	5.26 5.28	4.33 4.35

Further, condensation[26-28] of 5-(4-methylbenzylidene)-2-phenyl-5,6-dihydro-4*H*-[1,3]oxazin-6-one **2a** ($R_1 = R_2 = R_3 = H$ and $R_4 = CH_3$) with o-phenylenediamine in 1:1 molar ratio, in the presence of dry benzene yielded a crystalline compound **3a**. Based on spectral data and elemental analysis, the compound obtained was assigned the structure as 4-(4-methylbenzylidene)-1-phenyl-3,4-dihydropyrimido[1,6-a]benzimidazole **3a** ($R^1 = R^2 = R^3 = H$ and $R^4 = CH_3$) in the IR spectrum of which the band due to δ-lactone carbonyl group was wanting and the presence of characterstic proton signals in ^{1}HNMR corresponding to those of the **2a** confirmed unequivocally the assigned structure of compound **3a**. Condensation of other differently substituted 5-benzylidene-2-aryl-5,6-dihydro-4*H*-[1,3]oxazin-6-one **2b-2h** with o-phenylenediamine in dry benzene yielded differently substituted 4-benzylidene-1-phenyl-3,4-dihydropyrimido[1,6-a] benzimidazoles **3b-3h** respectively in good yields Table 2. The structures of all these compounds were established by elemental analysis and spectral studies (IR, ^{1}HNMR and ^{13}CNMR).

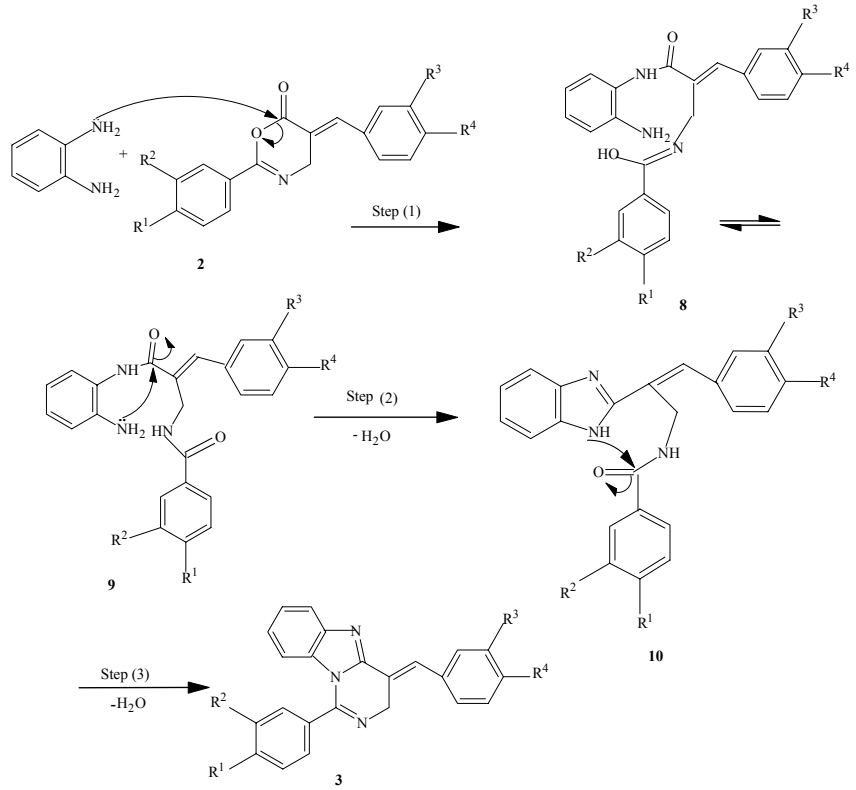
The mechanism for the reactions is outlined in Scheme 2 and Scheme 3.

Table 2. Differently substituted 4-benzylidene-1-phenyl-3,4-dihydropyrimido [1,6-a]benzimidazoles **3a-3h** with mp's., yields and mol. formulae

Compound	R	Mp's. (ºC)	Yield (%)	Mol. formulae (M^+)	Calcd. formula% Obsd. formula%		
					C	**H**	**N**
3a	$R^1 = R^2 = R^3 = H$, $R^4 = CH_3$	210-212	63	$C_{24}H_{19}N_3$	82.52 82.48	5.44 5.47	12.03 12.05
3b	$R^1 = CH_3$, $R^2 = R^3 = H$, $R^4 = OCH_3$	215-216	65	$C_{25}H_{21}N_3O$	79.15 79.18	5.54 5.56	11.08 10.08
3c	$R^1 = OCH_3$, $R^2 = R^3 = R^4 = H$	209	64	$C_{24}H_{19}N_3O$	78.90 78.85	5.20 5.28	11.50 11.47
3d	$R^1 = R^2 = OCH_3$, $R^3 = H$, $R^4 = CH_3$	218	66	$C_{26}H_{23}N_3O_2$	76.28 76.25	5.62 5.70	10.26 10.15
3e	$R^1 = R^2 = H$, $R^3 = R^4 = OCH_3$	223	67	$C_{25}H_{21}N_3O_2$	75.94 75.92	5.31 5.35	10.63 10.65
3f	$R^1 = CH_3$, $R^2 = H$, $R^3 = R^4 = OCH_3$	225	68	$C_{26}H_{23}N_3O_2$	76.28 76.25	5.62 5.60	10.26 10.28
3g	$R^1 = OCH_3$, $R^2 = R^3 = H$, $R^4 = CH_3$	216	66	$C_{25}H_{21}N_3O_2$	79.15 79.12	5.54 5.53	11.08 11.09
3h	$R^1 = R^2 = OCH_3$, $R^3 = R^4 = H$	219	67	$C_{25}H_{21}N_3O$	75.94 75.82	5.31 5.40	10.63 10.64



Scheme 2. Mechanism of formation of **2** from **1.**



Scheme 3. Mechanism of formation of **3** from **2.**

Pharmacology

On preliminary pharmacological screening all the 1,3-oxazines **2a-2h** and pyrimido [1,6-a]benzimidazole derivatives **3a-3h** have been found to be promising bronchodilatory and oxytocic agents having activities comparable to those of alkaloid vasicine and its natural and synthetic analogues. The detailed study of the evaluation of these biological activities is under active exploration from our research laboratory. The drugs employed in this study are 7,8,9,10-tetrahydroazepino[2,1-b]quinazolin-12(6*H*)-one; Aminophyllin injection I.P(Burroughs Wellcome & Co.); Histamine diphosphate (Sigma); Adrenaline tartarate (IP); Propanolol HCl (ICI); 5-hydroxytryptamine; and Egg albumin (BDH). The comparative SAR of various compounds[29] and the results of other details regarding these activities are being currently determined. All the pyrimido[1,6-a]benzimidazole derivatives 3a-3h have been found to be weakly to moderately active antimicrobial agents. Compounds **3b-3h** have been found to be highly promising, as regards as 'Tracheal smooth muscle activity' and 'Antitussive activity'.

Antimicrobial activity. The compounds **3a-3h** have been screened for their antifungal activity against Aspergillus, Penicillium and Cladosporium species. For antibacterial activity, these compounds have been screened against E.coli, Bacillus subtilis and Bacillus cereus. Both the activities were evaluated at the same concentration of 1000μg and through well diffusion technique. The standard antifungal agent fluconazole and the antibacterial agent norfloxacin were also screened under similar conditions for a comparative study. The inhibition zones formed were measured in mm and are listed in Table 3**.**

Table 3. Antimicrobial activity of compounds **3a-3h**

Antibacterial activity				Antifungal activity		
Compd.No	E.coli	B.subtilis	B.cereus	A.niger	P.species	C.species
3a	16	13	19	19	15	18
3b	13	12	17	15	13	16
3c	17	10	20	20	17	17
3d	14	11	18	16	16	18
3e	18	15	18	19	18	18
3f	20	12	17	14	16	16
3g	20	13	15	20	14	20
3h	19	14	14	17	18	19
NR	28	26	28	----	----	----
Flu	----	----	----	32	25	23

Note: 10mm, inactive; 11-15mm, weakly active; 16-20mm, moderately active. NR: Norfloxacin Flu: Fluconazole

Broncodilatory activity

Tracheal smooth muscle activity. Preparation of tissue was similar to that described by Castillow and de Beer[30] except that the tracheal ring was opened by severing the cartilage. Guineapigs (350-500g) of either sex were sacrificed by a blow to the head and the tracheae rapidly excised. The tracheal chain was prepared and suspended in a 20 mL tissue bath containing Krebs-Henselet solution (KHS) continuously aerated with 95% O_2 and 5% CO_2 and maintained at 37°. The composition (mM) of (KHS) was NaCl 118, KCl 4.7, $MgSO_4.7H_2O$ 1.2, $CaCl_2$ 2.2, KH_2PO_4 1.2, $NaHCO_3$ 24.9 and (+)-glucose 11.1. The responses were recorded isotonically on a kymograph. The tissue was adjusted to an initial tension of 1.5 g and allowed to equilibrate (60-90) minutes. Relaxation effect of the drug was studied on tracheal chain precontracted with histamine diphosphate (1×10^{-6} g/mL) or acetylcholine chloride (1×10^{-6} g/mL). The test drugs were added 8 minutes after the tonic contraction reached plateau. The responses were calculated as per cent to relaxing of precontracted muscle back to base line tension (10% relaxation). If there was relaxation to muscle slightly below the base line it was also taken as 100% relaxation.

Antitussive activity. Kobayshi's[31] method was used in this study. Guineapigs (300-400 g) were aneasthetised by I/P urethane (6.5 mL/kg; 25%) and fixed in dorsal position. The trachea was exposed and a small incision made at a distance of 1.5 cm from the clavicle. A fine and very thin polythene tube was inserted into the incision as deep as 3 cm to give the stimulus. The stimulus was applied two times before and 15, 30, 45, 60, 90 and 120 minutes after the drug dministration by oral route. If no coughing occurred in 2 or more out of 5 trails after drug administration, the drug was estimated as effective. Results are shown in Table 4.

Experimental Section

General Procedures. The melting points were determined in open capillary tubes in melting point apparatus and are uncorrected. The purity of the products was checked on TLC plates coated with silica gel-G and detected by iodine vapours. The IR spectra were recorded on Perkin Elmer Infrared model S99-B and on Shimdzu IR-435 spectrophotometer (υ_{max} in cm^{-1}). ^{1}H NMR and ^{13}C NMR spectra were recorded on a varian unity 200 MHz NMR spectrophotometer using ppm on δ scale). Elemental analysis was performed on a simple CHNS analyzer (model: CHNS-932, LECO Corporation, USA; IR Technology Services Pvt. Ltd. Noida, U.P, India.)

Table 4. Broncodilatory and antitussive activities of compounds **3a-3h**

Compd.	*In vitro* guineapig trachea % relaxation			Antitussive activity (guineapig)	
	Histamine	Acetylcholine	Concn (μ/mL)	% cough inhibition	Dose mg/kg
3a	20	–	–	–	10
3b	40	30	10	40	10
3c	30-50 50-70 100	20-30 30-60 80-100	3 10 30	40 60 60	10
3d	80	–	30	100	10
3e	10	10-15	3	100	10
3f	–	30	10	60	10
3g	20	10-15	30	60	10
3h	40-50	40-50	30	100	10
Bromhexine hydrochloride	_	_	_	40-80 100	2 4

Benzoylation of β–alanine and 3-benzoyl aminopropanoic acids 1a-1d. Dissolved (0.33 mol) β–alanine (CDH, Laboratory reagents Pvt. Ltd.) in 250 mL of 10% NaOH solution contained in a conical flask. Added 45 mL (0.385 mol) of corresponding benzoyl chloride in five portions to the solution. Stoppered the vessel and shook vigorously after each addition till all the acid chloride had reacted. Transfered the solution to a beaker and added few gms of crushed ice to it. Added concentrated HCl slowly with stirring till the mixture was acidic to congo red paper. Collected the resulting crystalline precipitates of substituted 3-benzoylaminopropanoic acids **1a-1d** by filtration, recrystallised the dried product in each case from boiling water (about 500 mL) and dried them in an oven.

Synthesis of differently substituted-5,6-dihydro-4*H*-[1,3]oxazin-6-ones 2a-2h. A mixture of 3-benzoylaminopropanoic acid (0.25 mol), aromatic aldehyde (CDH, Laboratory reagents Pvt. Ltd.) (0.25 mol), acetic anhydride (0.75 mol) and anhydrous sodium acetate (0.25 mol) was taken in a 250 mL conical flask and heated on an electric hot plate with constant shaking. As soon as the mixture liquified completely, transfered the flask to a water-bath and heated for 2 hour. Then added 100 mL of ethanol slowly to the contents of the flask and allowed the mixture to stand overnight. Filtered the crystalline product in each case, washed with ice-cold alcohol, washed with 25 mL of boiling water and dried at 100 °C when **2a-2h** were obtained.

Synthesis of differently substituted-3,4-dihydropyrimido [1,6-a]benzimidazole 3a-3h. Added (0.25 mol) of substituted 5,6-dihydro-4H-[1,3]oxazin-6-ones **2a-2h** and (0.25 mol) of o-phenylenediamine (Thomas Baker Chm. Ltd. Mumbai, India) in dry benzene in a 250 mL round bottom flask and refluxed on a water-bath initially for two hours. Then refluxing was continued for a further period of 10 minutes by the addition of few drops of acetic acid. Within few minutes the colourless compound that separated out in each reaction was filtered and recrystallised from acetic acid to give **3a-3h**.

Spectral data

5-(4-Methylbenzylidene)-2-phenyl-5,6-dihydro-4*H*-[1,3]oxazin-6-one (2a). IR (KBr, υ, cm^{-1}): 3065 (C-H, aromatic); 2825 (C-H, aliphatic); 1785 (C=O); 1685 (C=N); 1520 (C⋯⋯C of aromatic ring); 1454 (C=H bending of methylene); 1072 (C-O-C). ^{1}HNMR($CDCl_3$) : δ 7.2-7.58 (m, 9H, Ar-Hs), 5.85 (s, 1H, =CH-), 2.95 (s, 2H, CH_2), 2.2 (s, 3H, CH_3). ^{13}CNMR ($CDCl_3$) : 171 (C_6) ; 159 (C_2) ; 137.1 (-CH= of benzylidene) ; 135.2 ($C_1^{//}$) ; 133.5 ($C_1^{/}$) ; 130.5 ($C_4^{//}$) ; 129.5 (2×CH) ; 127.9 (2×CH) ; 127.6 (2×CH) ; 127.2 ($C_4^{/}$) ; 125.4 (2×CH) ; 125.1 (C_5) ; 44.7 (C_4) ; 14.59 (CH_3 at $C_4^{/}$).

5-(4-Methoxybenzylidene)-2-(4-methylphenyl)-5,6-dihydro-4*H*-[1,3]oxazin-6-one (2b). IR (KBr, υ, cm^{-1}): 3068 (C-H, aromatic); 2828 (C-H, aliphatic); 1770 (C=O); 1670 (C=N); 1525 (C⋯⋯C of aromatic ring); 1460 (C=H bending of methylene); 1075 (C-O-C); 1025 (C-O). ^{1}HNMR($CDCl_3$): δ 7.14-7.59 (m, 8H, Ar-Hs), 5.80 (s, 1H, =CH-), 3.70 (s, 3H, OCH_3), 2.92 (s, 2H, CH_2), 2.24 (s, 3H, CH_3).

5-Benzylidene-2-(4-methoxyphenyl)-5,6-dihydro-4*H*-[1,3]oxazin-6-one (2c). IR (KBr, υ, cm^{-1}): 3062 (C-H, aromatic); 2827 (C-H, aliphatic); 1771 (C=O); 1672 (C=N); 1529 (C⋯⋯C of aromatic ring); 1460 (C=H bending of methylene); 1075 (C-O-C); 1028 (C-O). ^{1}HNMR($CDCl_3$) : 7.12-7.50 (m, 9H, Ar-Hs), 5.82 (s, 1H, =CH-), 3.68 (s, 3H, OCH_3), 2.9 (s, 2H, CH_2).

5-(4-Methylbenzylidene)-2-(3,4-dimethoxyphenyl)-5,6-dihydro-4*H*-[1,3]oxazin-6-one (2d). IR (KBr, υ, cm^{-1}) : 3060 (C-H, aromatic); 2830 (C-H, aliphatic); 1775 (C=O); 1674 (C=N); 1530 (C⋯⋯C of aromatic ring); 1465 (C=H bending of methylene); 1076 (C-O-C); 1030 (C-O). ^{1}HNMR($CDCl_3$) : δ 7.12-7.48 (m, 7H, Ar-Hs), 5.92 (s, 1H, =CH-), 3.74 (s, 3H, OCH_3), 3.68 (s, 3H, OCH_3), 2.92 (s, 2H, CH_2), 2.22 (s, 3H, CH_3).

5-(3,4-Dimethoxybenzylidene)-2-phenyl-5,6-dihydro-4*H*-[1,3]oxazin-6-one (2e). IR (KBr, υ, cm^{-1}): 3062 (C-H), aromatic); 2832 (C-H, aliphatic); 1774 (C=O); 1672 (C=N); 1528 (C⋯⋯C of aromatic ring); 1468 (C=H bending of methylene); 1075 (C-O-C); 1028 (C-O). ^{1}HNMR($CDCl_3$) : δ 7.01-7.14 (m, 8H, Ar-Hs), 5.90 (s, 1H, =CH-), 3.72 (s, 3H, OCH_3), 3.64 (s, 3H, OCH_3), 2.91 (s, 2H, CH_2).

5-(3,4-Dimethoxybenzylidene)-2-(4-methylphenyl)-5,6-dihydro-4*H*-[1,3]oxazin-6-one (2f). IR (KBr, υ, cm^{-1}) : 3062 (C-H, aromatic); 2832 (C-H, aliphatic); 1775 (C=O); 1675 (C=N); 1526 (C⋯⋯C of aromatic ring); 1465 (C=H bending of methylene); 1075 (C-O-C); 1030 (C-O).

^{1}HNMR($CDCl_3$) : δ 7.02-7.15 (m, 7H, Ar-Hs), 5.78 (s, 1H, =CH-), 3.72 (s, 3H, OCH_3), 3.68 (s, 3H, OCH_3), 2.84 (s, 2H, CH_2), 2.21 (s, 3H, CH_3).

5-(4-Methylbenzylidene)-2-(4-methoxyphenyl)-4,5-dihydro-4*H*-[1,3]oxazin-6-one (2g). IR (KBr, υ, cm^{-1}): 3064 (C-H, aromatic); 2834 (C-H, aliphatic); 1775 (C=O); 1672 (C=N); 1525 (C⋯⋯C of aromatic ring); 1467 (C=H bending of methylene); 1075 (C-O-C); 1028 (C-O). ^{1}H NMR($CDCl_3$) : δ 7.01-7.19 (m, 8H, Ar-Hs), 5.80 (s, 1H, =CH-), 3.74 (s, 3H, OCH_3), 2.80 (s, 2H, CH_2), 2.24 (s, 3H, CH_3).

5-Benzylidene-2-(3,4-dimethoxyphenyl)-5,6-dihydro-4*H*-[1,3]oxazin-6-one (2h). IR (KBr,υ,cm^{-1}): 3062 (C-H, aromatic); 2832 (C-H, aliphatic); 1772 (C=O); 1675 (C=N); 1525 (C⋯⋯C of aromatic ring); 1468 (C=H bending of methylene); 1072 (C-O-C); 1025 (C-O). ^{1}HNMR($CDCl_3$) : δ 6.98-7.12 (m, 8H, Ar-Hs), 5.80 (s, 1H, =CH-), 3.70 (s, 3H, OCH_3), 3.64 (s, 3H, OCH_3), 2.82 (s, 2H, CH_2).

4-(4-Methylbenzylidene)-1-phenyl-3,4-dihydropyrimido[1,6-*a*]benzimidazole (3a). IR (KBr, υ, cm^{-1}): 3047 (C-H, aromatic); 2920 (C-H, aliphatic); 1520 (C⋯⋯C of aromatic ring); 1458 (C=N); 1272 (C-N). ^{1}HNMR ($CDCl_3$): δ 7.2-7.60 (m, 13H, Ar-Hs), 5.79 (s, H, =CH-), 2.80 (s, 2H, CH_2), 2.25 (s, 3H, CH_3). ^{13}CNMR ($CDCl_3$) : 158 (C_1) ; 139.4 (C_{4a}) ; 138.5, 137.4, 137.2 (3×C) ; 136.9 ($C_4^{/}$) ; 133.5 (C_4) ; 131.7 ($C_1^{/}$) ; 130.4 ($C_4^{//}$) ; 129.2, 128.4 (2×CH) ; 128.0, 127.5 (4×CH) ; 124.5 (-CH= of benzylidene) ; 122.9 (2×CH) ; 115.4 (2×CH) ; 58.8 (C_3) ; 20.7 (CH_3 at $C_4^{/}$).

4-(4-Methoxybenzylidene)-1-(4-methylphenyl)-3,4-dihydropyrimido[1,6-*a*]benzimidazole (3b). IR (KBr, υ, cm^{-1}): 3045 (C-H, aromatic); 2925 (C-H, aliphatic); 1520 (C⋯⋯C of aromatic ring); 1459 (C=N); 1275 (C-N); 1075 (C-O). ^{1}HNMR($CDCl_3$) : δ 7.2-7.58 (m, 12H, Ar-Hs), 5.80 (s, 1H, =CH-), 3.67 (s, 3H, OCH_3), 2.82 (s, 2H, CH_2), 2.2 (s, 3H, CH_3). ^{13}CNMR ($CDCl_3$) : 161.2 ($C_4^{/}$) ; 158 (C_1) ; 140.0 ($C_4^{//}$) ; 139.4 (C_{4a}) ; 134.3 ($C_1^{//}$) ; 138.5, 137.4, (2×C) ; 133.5 (C_4) ; 129.2, 128.9 (2×CH) ; 127.2, 127.0 (3×CH) ; 124.5 (-CH= of benzylidene) ; 122.9 (2×CH) ; 114.0 (2×CH) ; 115.4 (2×CH) ; 58.8 (C_3) ; 56.0 (OCH_3 at $C_4^{/}$) ; 20.7 (CH_3 at $C_4^{/}$).

4-Benzylidene-1-(4-methoxyphenyl)-3,4-dihydropyrimido[1,6-*a*]benzimidazole (3c). IR (KBr, υ, cm^{-1}) : 3048 (C-H, aromatic) ; 2928 (C-H, aliphatic); 1527 (C⋯⋯C of aromatic ring); 1458 (C=N); 1278 (C-N); 1078 (C-O). ^{1}HNMR ($CDCl_3$) : δ 6.92-7.10 (m, 13H, Ar-Hs), 5.74 (s,1H, =CH-), 3.74 (s, 3H, OCH_3), 2.81 (s, 2H, CH_2). ^{13}CNMR ($CDCl_3$) : 164.3 ($C_4^{//}$) ; 158 (C_1) ; 139.4 (C_{4a}) ; 138.5, 137.4 (2×C) ; 136.9 ($C_4^{/}$) ; 133.5 (C_4) ; 131.9 ($C_1^{/}$) ; 130.0 ,129.6 (3×CH) ; 128.0, 127.5, 127.8 (5×CH) ; 124.5 (-CH= of benzylidene) ; 122.9 (2×CH) ; 114.2 , 115.4 (4×CH) ; 58.8 (C_3) ; 56.0 (OCH_3 at $C_4^{//}$).

1-(3,4-Dimethoxyphenyl)-4-(4-methylbenzylidene)-3,4-dihydropyrimido[1,6-*a*]benzimidazole (3d). IR (KBr, υ, cm^{-1}): 3085 (C-H, aromatic); 2950 (C-H, aliphatic); 1538 (C⋯⋯C of aromatic ring); 1480 (C=N); 1280 (C-N); 1079 (C-O). ^{1}HNMR($CDCl_3$) : 6.85-7.14 (m, 11H, Ar-Hs), 5.78 (s, 1H, =CH-), 3.75 (s, 3H, OCH_3), 3.68 (s, 3H, OCH_3), 2.78 (s, 2H, CH_2), 2.19 (s, 3H, CH_3). ^{13}CNMR ($CDCl_3$) : 158 (C_1) ; 149.9 ($C_4^{//}$) ; 147.7 ($C_3^{//}$) ; 139.4 (C_{4a}) ; 138.5 , 137.4 (2×C) ; 136.9 ($C_4^{/}$) ; 133.5 (C_4) ; 131.9 ($C_1^{/}$) ; 130.6 ($C_1^{//}$) ; 129.1 (2×CH) ; 126.1 (2×CH) ;

124.5 (-CH= of benzylidene) ; 122.9 , 122.3 (3×CH) ; 116.3 , 115.4 , 115.2 (4×CH) ; 56.3 (2×C ; OCH_3 at $C_3^{//}$,$C_4^{//}$) ; 20.9 (CH_3 at $C_4^{/}$).

4-(3,4-Dimethoxybenzylidene)-1-phenyl-3,4-dihydropyrimido[1,6-*a*] benzimidazole (3e). IR (KBr, υ, cm^{-1}): 3080 (C-H, aromatic); 2948 (C-H, aliphatic); 1535 (C⋯⋯C of aromatic ring); 1475 (C=N); 1278 (C-N); 1075 (C-O). ^{1}HNMR($CDCl_3$) : 6.89-7.15 (m, 12H, Ar-Hs), 5.73 (s, 1H, =CH-), 3.72 (s, 3H, OCH_3), 3.65 (s, 3H, OCH_3), 2.76 (s, 2H, CH_2). ^{13}CNMR ($CDCl_3$) : 158 (C_1) ; 147.5 , 146.8 (2×C) ; $C_3^{/}$; 139.4 (C_{4a}) ; 138.5 , 137.4 , 137.2 (3×C) ; 133.5 (C_4) ; 130.4 ($C_4^{//}$) ; 129.2 , 128.4 , 128.2 (5×CH) ; 124.5 (-CH= of benzylidene) ; 122.9 (2×CH) ; 115.4 , 115.0 (3×CH) ; 58.8 (C_3) , 56.3 (2×C ; OCH_3 at $C_3^{/}$, $C_4^{/}$).

4-(3,4-Dimethoxybenzylidene)-1-(4-methylphenyl)-3,4-dihydropyrimido[1,6-*a*]benzimidazole (3f). IR (KBr, υ, cm^{-1}): 3082 (C-H aromatic); 2950 (C-H, aliphatic); 1538 (C⋯⋯C of aromatic ring); 1470 (C=N); 1275 (C-N); 1072 (C-O). ^{1}HNMR($CDCl_3$) : δ 6.82-7.15 (m, 11H, Ar-Hs), 5.71 (s, 1H, =CH-), 3.71 (s, 3H, OCH_3), 3.67 (s, 3H, OCH_3), 2.74 (s, 2H, CH_2), 2.22 (s, 3H, CH_3). ^{13}CNMR ($CDCl_3$) : 158 (C_1) ; 147.5 , 146.8 (2×C) ; 140.0 ($C_4^{//}$) ; 139.4 (C_{4a}) ; 137.4 , 137.2 (2×C) ; C_{9a} ; 134.3 ($C_1^{//}$) ; 133.5 (C_4) ; 129.3 , 128.9 , (4×CH) ; 124.5 (-CH= of benzylidene) ; 122.9 (2×CH) ; 119.5 ($C_6^{/}$) ; 115.4 , 115.0 (3×CH) ; 58.8 (C_3) , 56.3 (2×C ; OCH_3 at $C_3^{/}$, $C_4^{/}$) ; 20.9 (CH_3 at $C_4^{//}$).

1-(4-Methoxyphenyl)-4-(4-methylbenzylidene)-3,4-dihydropyrimido[1,6-*a*]benzimidazole (3g). IR (KBr, υ, cm^{-1}): 3080 (C-H aromatic); 2942 (C-H, aliphatic); 1530 (C⋯⋯C of aromatic ring); 1462 (C=N); 1270 (C-N); 1065 (C-O). ^{1}HNMR($CDCl_3$): δ 6.81-7.15 (m, 12H, Ar-Hs), 5.75 (s, 1H, =CH-), 3.74 (s, 3H, OCH_3), 2.70 (s, 2H, CH_2), 2.22 (s, 3H, CH_3). ^{13}CNMR ($CDCl_3$) : 164.3 ($C_4^{//}$) ; 158 (C_1) ; 139.4 (C_{4a}) ; 138.5 , 137.4 , (2×C) ;136.9 ($C_4^{/}$) ; 133.5 (C_4) ; 131.9 ($C_1^{/}$) ; 130.0 , 129.6 (3×CH) ; 129.1 (2×CH) ; 126.1 (2×CH) ; 124.5 (-CH= of benzylidene) ; 122.9 (2×CH) ; 114.2 , 115.4 (4×CH) ; 58.8 (C_3) ; 56.0 (OCH_3 at $C_4^{//}$) ; 20.6 (CH_3 at $C_4^{/}$).

4-Benzylidene-1-(3,4-dimethoxyphenyl)-3,4-dihydropyrimido[1,6-*a*]benzimidazole (3h). IR (KBr, υ, cm^{-1}): 3092 (C-H, aromatic); 2956 (C-H, aliphatic); 1543 (C⋯⋯C of aromatic ring); 1482 (C=N); 1279 (C-N); 1078 (C-O). ^{1}HNMR ($CDCl_3$): δ 7.21-7.40 (m, 9H, Ar-Hs), 6.70-6.75 (m, 3H, Ar-Hs), 5.34 (s, 1H, =CH-), 3.72 (s, 3H, OCH_3), 3.68 (s, 3H, OCH_3), 2.78 (s, 2H, CH_2). ^{13}CNMR ($CDCl_3$) : 158 (C_1) ; 149.9 ($C_4^{//}$) ; 147.7 ($C_3^{//}$) ; 139.4 (C_{4a}) ; 138.5 , 137.4 (2×C); 136.9 ($C_4^{/}$) ; 133.5 (C_4) ; 131.9 ($C_1^{/}$) ; 130.6 ($C_1^{//}$) ; 128.0 , 127.5 , 127.8 (5×CH); 124.5 (-CH= of benzylidene) ; 122.9 , 122.3 (3×CH) ; 116.3 , 115.4 , 115.2 (4×CH); 56.3 (2×C ; OCH_3 at $C_3^{//}$,$C_4^{//}$).

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