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Synthesis and Pharmacological Evaluation of 2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate Derivatives as Alpha1 Receptor Blockers

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Abstract: Alpha receptor play major role in the hypertension process and the inhibition of α1 receptor by alpha receptor blockers has been a common target of antihypertensive drug discovery. The present study deal with the synthesis of novel dihydropyrimidinone (DHPM) derivatives from the reaction of N-substituted piperazine and substituted dihydropyrimidinone was performed. To study SAR of dihydropyrimidinone derivatives we introduced electron releasing, electron withdrawing substitution on phenyl ring attached to piperazine scaffold and also the different linkers like SO_2 and C=O between phenyl and piperazine ring were used. All compounds were found to be good to moderately good active. Compound **7g** was most found to be most active from the result of pharmacological evaluation among the all the DHPM derivatives and it was merely same as active as standard drug prazosin. Structure activity relationships of these series of compounds showed that piperazine ring attached to DHPM instead of substituted aromatic amine were responsible for increasing binding affinity for α1A receptor. The SO_2 bridge between phenyl ring and piperazine with electron releasing substituent increases α1A binding affinity. This work can be guidance for further development of DHPM moiety to get potent α1A receptor inhibitor antihypertensive agent.
Keywords: Alpha1 receptor blocker, antihypertensive agents, dihydropyrimidinone, piperazine.

Introduction

Hypertension is one of the most serious health problems of modern world with continuous rise in the number of patients. Various classes of antihypertensive drugs are currently available for treating hypertension. Reduction of the blood pressure by 5 mmHg can decrease the risk of stroke by 34%, of ischemic heart disease by 21%, and reduce the likelihood of dementia, heart failure, and mortality from cardiovascular disease. Diuretics, Adrenergic agonists, Adrenergic antagonists, Calcium channel blocker, ACE inhibitors etc are frequently used[1,2]. Selective α1-adreno receptor antagonists though have many advantages in the management of arterial hypertension. Existence of multiple α1-adreno receptor subtype hold great promise for discovery and development of more specific and selective drug molecule by targeting only one α1-adreno receptor subtype at a time and thus relative less side effects[3]. Three type of α_1 adrenoreceptor α_{1A}, α_{1B}, α_{1D} have recently been identified with varying tissue distribution. α_{1A} receptors are localized in Heart, lever and Vas deferens. α_{1A}

receptors mainly present in lower urinary tract tissue[2]. Thus the agents that inhibit α_{1A} receptors over α_{1B}, α_{1D} should display a better therapeutic profile, particularly in terms of cardio vascular effects.
Dihydropyrimidone are well known for their wide range of bioactivities and their application in the field of drug research such as Adrenoceptor antagonists, calcium channel modulator, mitotic kinesin inhibitor, Antibacterial agents, and anti-inflammatory agents[4]. In earlier studies niguldipine (DHP containing $\alpha 1_A$ blocker) like molecule SNAP5089 & SNAP5540 were developed. DHP (dihydropyridine) was further replaced by DHPM (Dihydropyrimidinone) due to improved pKa profile. SNAP6201 is a very good example of that shows good binding affinity and excellent subtype selectivity 300 fold for the $\alpha 1_A$ receptor, no cardiovascular effect and good pharmacodynamic profile[5,6]. After the further study of these scaffolds, it was found that Dihydropyrimidone offers two logical site of attachment of piperidine containing side chain. The first is at N-3 of the DHPM, exemplified by A, and compounds containing this general structure have been extensively documented as selective α1a antagonists. The success of this modification suggests that the exact structure of the central heterocycle is not critical and that the other mode of attachment of the piperidine containing side chain via amide bond formation of the DHP C-5 carboxylate might also provide potent and selective compounds[7].
This line of reasoning led to the preparation of B which was found to have Ki values of 2.9, 537, and 1513 nM vs. the α1a, α 1b, and α 1d receptors. The diverse types of biological activities associated with dihydro pyrimidone derivatives and their interesting chemistry prompted us to synthesize novel dihydro pyrimidone derivatives as selective $\alpha 1_A$ receptor blocker.

Experimental

Materials and Methods:

All the chemicals of synthetic grade procured from SD fine chemicals, Baroda, India. Melting points of the synthesized compounds were determined in open capillaries using Veego Melting Point apparatus, Model VMP-D (Veego India Ltd, Mumbai, India) and are uncorrected. Infrared spectra were recorded using Kbr pellets on SHIMADZU – FT – IR 8400S instrument. Mass spectra were recorded on Perkin-Elmer LC-MS PE Sciex API/65 spectrophotometer. The ^{1}H-NMR spectra were recorded on Brucker Avance- 300(300 MHz) model spectrophotometer in $CDCl_3$ and DMSO as solvent and TMSi as internal standard with ^{1}H resonant frequency of 300MHz.The chemical shift were measured in δ ppm downfield from internal standard (TMSi) at δ=0.The TLC was performed on alumina silica gel 60 F_{254} (Merck). The elemental analysis was done on Elementar Vario EL III Carlo Erba 1108 and was in well accordance with structures assigned to the compounds. All compounds gave C, H and N analysis with in ±0.4% of the theoretical values.

Chemistry:

The present synthetic strategy begins with the synthesis of chlorethyl acetoacetate (3) which was synthesized by reacting ethyl acetoacetate(1) with 1-chloro ethanol(2), using toluene as solvent[8]. The synthesis of dihydropyrimidone ring (5) was done by biginelli reaction in which Chloroethyl acetoacetate (3) reacted with urea and p-nitro benzaldehyde (4) with the help of catalyst boric acid, using glacial acetic acid as solvent[9]. Finally Synthesized dihydropyrimidone ring condensed with n-substituted piperazine (6) or substituted aniline with help of N, N-dimethyl formamide to give novel dihydropyrimidone derivatives (7a-g) and (8a,b) (scheme-1) .

General procedure for the preparation of compounds:

Preparation of 2-chloroethyl 6-methyl-4-(4-nitrophenyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate

A solution of the p-nitro benzaldehyde (3mmol), 1, 3-dicarbonyl compound (3mmol), urea (3.6 mmol), and H_3BO_3 (0.6 mMol), in glacial acetic acid (10 ml) is heated at 100^0C, while stirring for 3 hr. The solid was separated after pouring reaction mixture at room temperature in to 500 ml ice water. The products was filtered by vacuum filter washed with Methanol solvent.

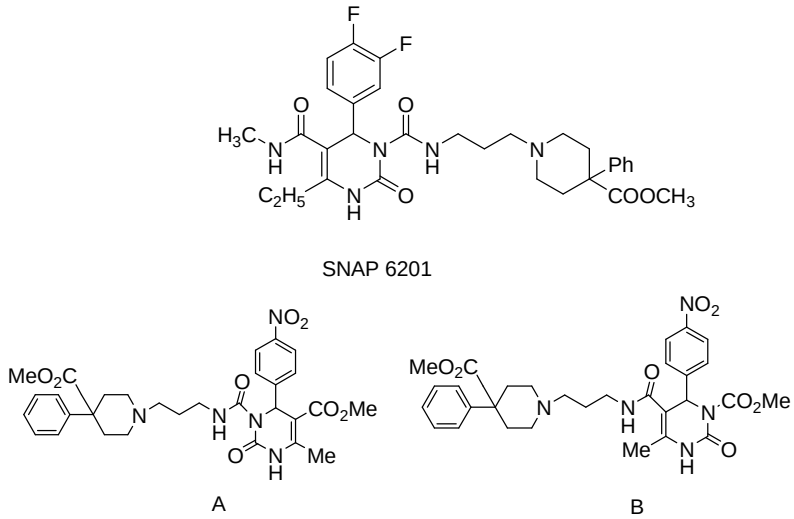


Fig. 1. Lead molecules having 1,2,3,4 tetrahydropyrimidinone scaffold as $\alpha 1_A$ receptor blockers

General method for synthesis of final products (7a-7g, 8a, 8b))

Equimolar quantity of N-substituted piperazine or substituted aniline in DMF (25 ml) refluxed with 2-chloroethyl 6-methyl-4-(4-nitrophenyl)-2-oxo-1, 2, 3, 4-tetrahydropyrimidine-5-carboxylate for 3-5h at about 110-130ºC.The reaction mixture was cooled at room temperature and poured into 500 ml ice-cold water. Precipitates then obtained were filtered and purified by washing with water and methanol and dried.

2-(4-benzoylpiperazine-1-yl) ethyl6-methyl-4-(4-nitrophenyl) -2-oxo-1, 2, 3, 4-tetrahydropyrimidine-5-carboxylate (7a)

reddish yellow product: yield 71%; m.p.221-223°C; IR (KBr,υ cm^{-1}) : 1629 (-C=O), 1490 (N-O asymmetric stretch), 1575 (C-N Stretch), 3142 (C-H Stretch);^{1}H-NMR(300 MHz, δ ppm, DMSO):8.22-8.25(d,1H,-NH), 7.51-8.20(m,9H,Ar-H), 2.52-3.43(t,8H,piperazine),6.43-6.48(s,1H,-NH), 3.5-4.42(t,4H,-CH_2), 2.27-2.34(s,3H,-CH_3),and MS: m/z 494.26(M+1).

2-(4-(4-methoxy phenyl) piperazine-1-yl) ethyl6-methyl-4-(4-nitrophenyl)-2-oxo-1,2 3,4-tetrahydro pyrimidine-5-carboxylate (7b)

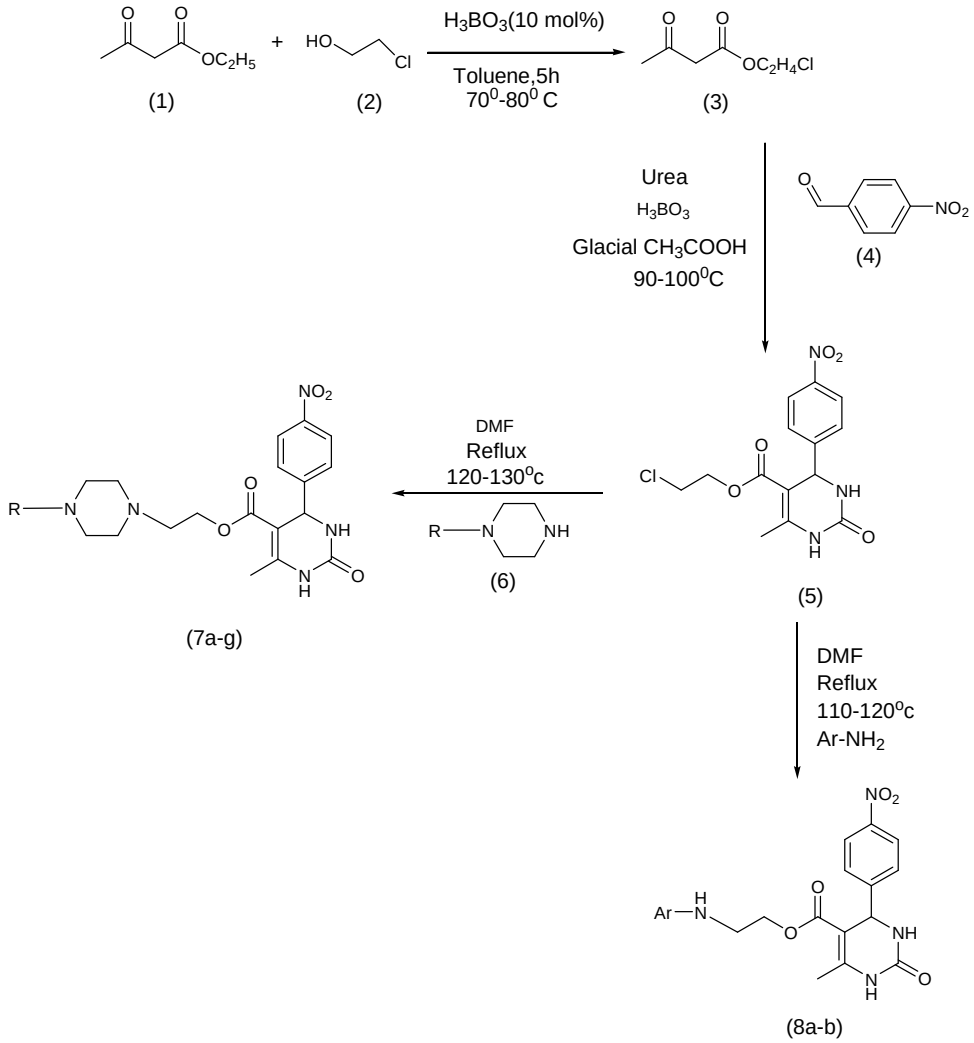
reddish yellow product: yield 74%; m.p. 113-115°C; IR (KBr,υ cm^{-1}) : 1629 (-C=O), 1490 (N-O asymmetric stretch), 1575 (C-N Stretch), 3142 (C-H Stretch),1310(C-O Stretch); ^{1}H-NMR(300 MHz, δ ppm, DMSO):8.22-8.25(m,1H,-NH),6.65-8.20(d,8H, Ar-H), 6.43-6.48(s,1H,-NH), 3.5-4.42(t,4H,-CH_2), 3.79-3.84(s,3H,O-CH_3), 2.52-3.43(t,8H,piperazine), 2.27-2.34(s,3H,-CH_3),and MS: m/z 496.38 (M+1).

2-(4-m-tolylpiperazine-1-yl)ethyl6-methyl-4-(4-nitrophenyl)-2-oxo-12,3,4-tetrahydropyrimidine-5-carboxylate (7c)

yellowish orange product: yield 80%; m.p 160-163°C; IR(KBr,υ cm^{-1}) : 1629 (-C=O), 1490(N-O asymmetric stretch), 1575 (C-N Stretch), 3142 (C-H Stretch);^{1}H-NMR(300 MHz, δ ppm, DMSO):8.22-8.25(d,1H,-NH), 6.47-8.20(m,8H, Ar-H), 6.43-6.48(s,1H,-NH), 2.97-4.42(t,4H,-CH_2), 2.52-3.43(t,8H,piperazine), 2.13-2.27(s,6H,-CH_3),and MS: m/z 480.02 (M+1).

2-(4-o-tolylpiperazin-1-yl)ethyl6-methyl-4-(4-nitrophenyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (7d)

Yellowish orange: yield 74%; m.p 194-198°C; IR(KBr,υ cm^{-1}) : 1629 (-C=O), 1490 (N-O asymmetric stretch), 1575 (C-N Stretch), 3142 (C-H Stretch);^{1}H-NMR(300 MHz, δ ppm, DMSO):8.22-8.25(d,1H,-NH),6.58-8.20(m,8H, Ar-H), 6.43-6.48(s,1H,-NH), 2.97-4.42(t,4H,-CH_2), 2.52-3.43(t,8H,piperazine), 2.13-2.27(s,6H,-CH_3),and MS: m/z 480.02 (M+1).



Scheme: 1 Synthesis of 1,2,3,4 tetrahydropyrimidinone derivatives

2-(4-(4-fluorophenyl) piperazine-1-yl) ethyl6-methyl-4-(4-nitrophenyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (7e)

Yellowish white product:yield 70.39%; m.p 142-146°C; IR(KBr,υ cm^{-1}) : 1629 (-C=O), 1490 (N-O asymmetric stretch), 1575 (C-N Stretch), 3142 (C-H Stretch),853(C-Cl Stretch); ^{1}H-NMR(300 MHz, δ ppm, DMSO):8.22-8.25(d,1H,-NH),6.7-8.20(m,8H, Ar-H), 6.43-6.48(s,1H,-NH), 2.97-4.42(t,4H,-CH_2), 2.52-3.43(t,8H,piperazine), 2.27-2.34(s,3H,-CH_3), and MS: m/z 484.23(M+1).

2-(4-(2, 4-dinitrophenyl)piperazine-1-yl)ethyl6-methyl-4-(4-nitrophenyl)-2-oxo-1,2,3,4-tetrahydro pyrimidine -5-carboxylate (7f)

Yellow product: yield 78%; m.p 236-238°C; IR(KBr,υ cm^{-1}) : 1490 (N-O asymmetric stretch), 1575 (C-N Stretch), 1629 (-C=O), 3142 (C-H Stretch); ^{1}H-NMR(300 MHz, δ ppm, DMSO):8.22-8.25(d,1H,-NH),7.25-8.20(m,7H, Ar-H), 6.43-6.48(s,1H,-NH), 2.97-4.42(t,4H,-CH_2), 2.52-3.43(t,8H,piperazine), 2.27-2.34(s,3H,-CH_3), and MS: m/z 556.17(M+1).

2-(4-(4-Acetamidophenylsulfonyl)piperazine-1-yl)ethyl6-methyl-4-(4-nitrophenyl)-2-oxo-1,2,3,4-tetrahydro pyrimidine-5-carboxylate (7g)

Yellow product: yield 69%; m.p 183-188°C; IR(KBr,υ cm^{-1}) :1339(-SO_2NH), 1490 (N-O asymmetric stretch), 1575 (C-N Stretch), 1629 (-C=O), 3142 (C-H Stretch),3315(N-H Stretch); ^{1}H-NMR(300 MHz, δ ppm, DMSO):8.67-8.71(s,1H,-NHCO), 8.22-8.25(d,1H,-NH),7.51-8.20 (m,8H, Ar-H),6.36-6.41(s,1H,-NH), 2.97-4.42(t,4H,-CH_2), 2.52-3.43(t,8H,piperazine), 2.06-2.34(s,6H,-CH_3), and MS: m/z 571.26(M+1).

2-(3-(Trifluromethyl) phenyl amino) ethyl 6-methyl-4-(4-nitrophenyl)-2-oxo-1, 2, 3, 4-tetrahydropyrimidine-5-carboxylate (8a)

Reddish yellow product:yield 65.23%; m.p 213-217°C; IR(KBr,υ cm^{-1}) : 863(C-Cl Stretch), 1490 (N-O asymmetric stretch), 1629 (-C=O), 3142 (C-H Stretch), 3315(N-H Stretch); ^{1}H-NMR(300 MHz, δ ppm, DMSO): 8.22-8.25(d,1H,-NH),6.46-8.20(m,8H, Ar-H),6.40-6.46(s,1H,-NH),3.57-4.55(t,4H,-CH_2),3.35-3.39 (s,1H,-NH) ,2.27-2.34(s,6H,-CH_3), and MS: m/z 465.34(M+1).

2-(4-(hydroxy)phenylamino)ethyl6-methyl-4-(4-nitrophenyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate(8b)

Greenish black product: yield 68.37%; m.p 189-194°C; IR(KBr,υ cm^{-1}) : 1490 (N-O asymmetric stretch), 1629 (-C=O), 3142 (C-H Stretch), 3315(N-H Stretch), 3632(O-H Stretch); ^{1}H-NMR(300 MHz, δ ppm, DMSO): 8.22-8.25(d,1H,-NH),6.60-8.20(m,8H, Ar-H),6.34-6.40(s,1H,-NH), 3.57-4.55(t,4H,-CH_2),4.03-4.09(s,1H,-OH), 2.66-2.72(s,1H,-NH),2.27-2.34(s,6H,-CH_3), and MS: m/z 413.28 (M+1).

Pharmacology:

All the synthesized compounds (7a-b, 8a, 8b) were screened for their antihypertensive activity on vasdeferens of Wistar rat. The study performed and approved by Institutional animal ethical committee of Shree S.K. Patel College of Pharmaceutical Education & Research. All the rats were maintained in essential condition of controlled temperature and humidity. The test compounds were prepared of different concentrations using DMSO. The pA_2 value defined as the negative logarithm to the base 10 of the molar concentration of antagonist that makes it necessary to double the concentration of agonist needed to elicit the original sub maximal response. And the term half maximal effective concentration (EC_{50}) refers to the concentration of a drug, which induces a response halfway between the baseline and maximum after some specified exposure time.

Antihypertensive activity[10,11]:

Wistar rat vasdeferens isolated after sacrificing by cervical dislocation. It was cleaned and made free from the surrounding fat and connective tissues. The Vas deference of 20 mm length and 3 mm width was mounted in organ bath (10ml) containing the Krebs henseleit buffer and pH 7.4 (maintained at the steady pH by checking every hour). The solution was continuously aerated with carbogen (95% O_2 and 5% CO_2) at 37ºC. The temperature of solutions was maintained at 37ºC till the end of the experiment with the help of heater placed in the organ bath by washing with KHS buffer at every 10 minutes. After one hour of equilibration, the preparation was challenged with 80 mM KCl until a platue was achieved by two equipotent response. This was done to check viability of the tissue. The 15 min of gaps should be kept in between each response so that it can come to its maximum resting state. Phenylephrine was then added in the range of concentrations into organ bath containing Krebs Henseleit solution until response reached a platue in contraction. Dose response curve (10^{-4}M) of Phenylephrine was constructed in control animals in the presence of different concentration of Phenylephrine. The concentration response curve of Phenylephrine (10^{-4}M) were also recorded in presence of prazosin and synthesized compounds. The changes in the contraction were recorded on the physiograph.

Data Analysis:

The EC_{50} (potency of antagonist) value was estimated in each individual concentration-response curve using the Boltzmann equation fit and converted to negative logarithm value (pD_2).

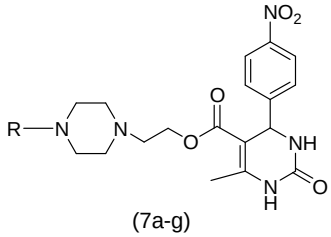
pD_2= -log (EC_{50})

Estimated pA_2 value were calculated according to the equation,

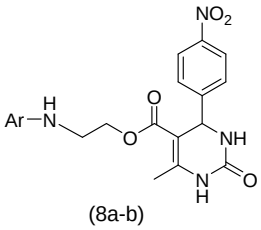
$pA_2 = -\text{Log}\,[B] + \text{Log}\,[(A_2)/(A_1) - 1]$

Where, Log [B] = Molar concentration of antagonist, (A_2) = EC_{50} of agonist in the presence of antagonist, (A_1) = EC_{50} of agonist in the absent of antagonist

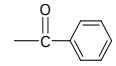
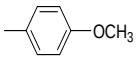
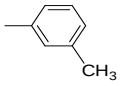
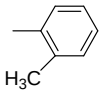
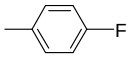
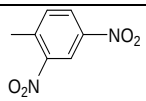
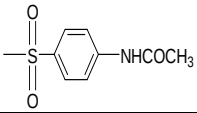
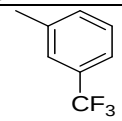
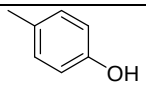
Table: 1 Physical and elemental data of the synthesized 1,2,3,4 tetrahydropyrimidinone derivatives



(7a-g)



(8a-b)

Sr. No	R	Yield[a] (%)	M.P.[b] (°c)	Mol. Formula/ Mol.Wt	Elem. analysis (%) (cal./found)		
					C	H	N
7a		70.89	221-223	$C_{25}H_{27}N_5O_6$ 493	60.22 60.14	5.31 5.15	14.56 14.48
7b		72.52	113-115	$C_{25}H_{29}N_5O_6$ 495	60.15 59.96	5.23 5.19	14.54 14.46
7c		80.12	160-163	$C_{25}H_{29}N_5O_5$ 479	62.58 62.49	6.02 5.98	14.60 14.52
7d		74.92	194-198	$C_{25}H_{29}N_5O_5$ 479	62.58 62.47	6.02 5.97	14.60 14.53
7e		70.39	142-146	$C_{24}H_{26}FN_5O_5$ 483	59.59 59.50	5.40 5.43	14.68 14.59
7f		78.82	236-238	$C_{24}H_{25}N_7O_9$ 555	51.22 51.19	4.37 4.28	17.24 17.19
7g		69.26	183-188	$C_{26}H_{30}N_6O_7S$ 570	54.69 54.68	5.27 5.19	14.67 14.62
8a		65.23	213-217	$C_{21}H_{29}N_3FO_5$ 464	54.31 54.25	4.12 4.07	12.06 12.10
8b		68.37	189-194	$C_{20}H_{20}N_4O_6$ 412	58.25 58.12	4.89 4.75	13.59 13.48

[a] Isolated yields, [b] Melting point were uncorrected

Table: 2 $\alpha 1_A$ receptor binding affinity of 1,2,3,4 tetrahydropyrimidinone derivatives

Compound no	EC_{50*}	pA_2
7a	$5.25*10^{-11}$	7.83
7b	$9.54*10^{-12}$	7.96
7c	$2.18*10^{-11}$	7.90
7d	$7.76*10^{-11}$	7.80
7e	$7.29*10^{-10}$	7.63
7f	$4.46*10^{-11}$	7.84
7g	$4.89*10^{-12}$	8.01
8a	$1.25*10^{-5}$	6.87
8b	$9.12*10^{-10}$	7.61
Prazosin (std)	$0.64*10^{-14}$	8.38
Terazosin (std)	$0.56*10^{-15}$	9.52

* EC_{50} = Effective Concentration

Result and Discussion

Selective α1-antagonists specifically $\alpha 1_{A,}$ which have been used to treat hypretension. α1- adrenergic receptor antagonists belongs to different class such as quinazoline, dihydropyridine, dihydropyrimidinone, benzoxazine and related compounds. Dihydropyrimidone have one of the most thoroughly studied classes of compounds with selective affinity for α1a-antagonists, So the dihydropyrimidone is an attractive lead showing good pharmacokinetic properties also.

Nine compounds were synthesized by a general procedure shown in scheme for anti hypertensive agents. All the compounds synthesized were insoluble in water and highly soluble in solvents like dimethylformamide, dimethylsulfoxide, and insoluble in benzene, n-hexane, petroleum ether and cyclohexane. The synthesized compounds were partially soluble in ethyl acetate.
Out of synthesized nine 1,2,3,4 tetrahydropyrimidinone derivatives, In which compounds, In 7(a) we introduced C=O bridge between piperazine and phenyl ring, compound 7(b), 7(c), 7(d) were substituted with electron releasing group containing phenyl ring attached to piperazine ring. Compound 7(e) and 7(f) was substituted with electron withdrawing group containing phenyl ring attached to piperazine ring. In compound 7(g) SO_2 Bridge between piperazine and phenyl ring and also phenyl ring substituted at para position by $NHCOCH_3$ group (electron releasing group) was introduced. And for understanding the role of piperazine we introduced substituted aniline instead of substituted piperazine in compound 8(a) and 8(b). EC_{50} and pA_2 value for the antihypertensive studies of the compounds (7a-g), 8(a-b) and the standard are shown in Table 2. The antihypertensive activity of the entire compounds showed good potencies which are comparable to standard drug prazosin. Synthesized compounds (7a), (7b), (7c), (7d), (7f) and (7g) showed good activity with pA_2 value ranging from 7.8-8.01. Particularly compound (7g), (7b), and (7c) showed very good activity ranging 8.01-7.9. And compound (7a), (7d), (7f), showed moderate activity ranging 7.8-7.84. While compound (7e) showed comparatively less activity 7.63. In the case of substituted primary aromatic amine in place of piperazine ring like 8a and 8b both showed low activities 6.87 and 7.61, respectively. Compound 7g was found to have good $\alpha 1_A$ receptor blocking activity. In general, SO_2 Bridge between piperazine and phenyl ring cause exceptionally increase in antihypertensive activity. And also summarize that compound with electron releasing group gave good antihypertensive activity. While compounds with electron withdrawing group showed moderate to low antihypertensive activity. And In the case of compound 8(a) and 8(b), activity of these compound revealed that piperazine ring might be involved in binding with the $\alpha 1_A$ adrenergic receptor for antihypertensive activity. Finally 1,2,3,4 tetrahydropyrimidinone, 2-carboxylate scaffold substituted with piperazine and SO_2 bridge at 5^{th} position bearing electron releasing group are supposed to be important pharmacophore for the alpha-1a receptor blocker for anti hypertensive therapy.

Conclusion

In conclusion, a series of 1,2,3,4 tetrahydropyrimidinone derivative was synthesized and evaluated for their antihypertensive activity. All the compounds were found to be moderate to good active. Compounds 7(b),7(c), and 7(g) showed very good activity. The compound 7(g) was found to be similar activity as standard drug prazosin. Piperazine ring containing compound showed better activity than substituted primary aromatic ring containing compound (8a, 8b). For $\alpha 1_A$ receptor blocking activity piperazine ring is necessary along with SO_2 Bridge between piperazine and phenyl ring with electron releasing groups. In future electron releasing group containing phenyl ring attached with piperazine with help of SO_2 bridge containing derivatives could be new pharmacophore for $\alpha 1_A$ adrenergic receptor blocking agents.

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