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Synthesis and Antihypertensive Activity of Some Quinazoline Derivatives

Harsha U. Patel, Ravi S. Patel, Chhaganbhai N. Patel
[1]Shri Sarvajanik Pharmacy College, Arvind Baug, Mehsana-384001, Gujarat, India.

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ABSTRACT

Quinazoline derivatives have been very well known for Antihypertensive activity. Seven new Quinazoline derivatives are synthesized by three steps. Purity of compound is checked by TLC monitoring. All synthesized compounds are confirmed by UV, IR, Mass and H^1NMR. All synthesized compound were screened for α_1-adrenergic receptor blocking activity. Amongst all synthesized compounds 4a & 4e showed better activity.

INTRODUCTION

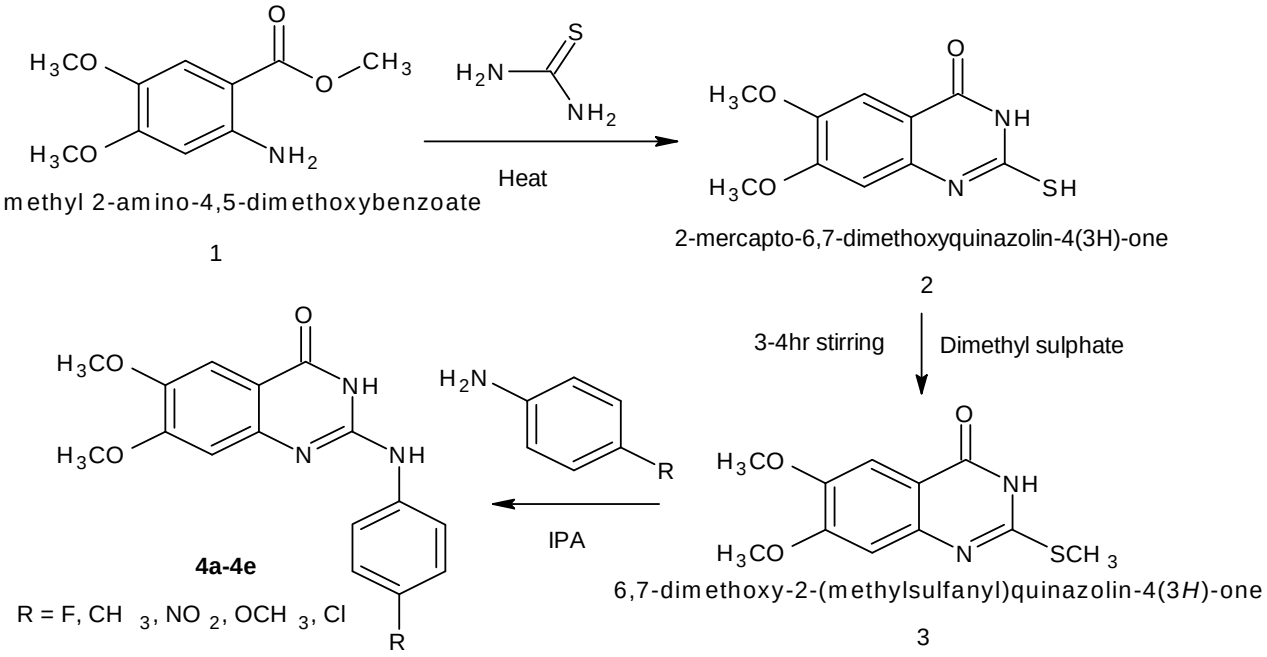
Quinazoline derivatives have been very well known for antihypertensive activity. Different quinazoline analogous having antihypertensive activity (eg. Prazosin, terazosin, doxazosin, bunazosin, tiodazosin, trimazosin and alfuzosin) are available in the market. They have many advantages like dictating both resistance and capacitance of blood vessels, favorable hemodynamic effects, virtual absence of reflux tachycardia, and maintenance of renal blood flow and glomerular filtration rate with intact auto regulation of noradrenaline due to non-blockade of presynaptic α_2–adr. These drugs are also useful in the treatment of Congestive Heart Disease (CHD), Variant or Prinzmetal's Angina, Raynauds disease, etc. From literature survey, several of quinazoline derivatives have been found to exhibit a wide spectrum of biological effects including antimicrobial, antitumour, antiviral, antiinflamatory, antihypertensive, α-1a adrenergic antagonist (Algarsamy *et al.*, 2007, Giardina et al.,1997, Jain *et al.*, 2008, 2010). So it was planned to synthesize newer quinazoline analogous and evaluate them for antihypertensive activity.

* *Corresponding Author*
Email: ravipatan251988@gmail.com

Experimental

The entire chemicals were supplied by S.D. Fine chem. (Mumbai), Sigma-Aldrich.Ltd., Finar chem. Ltd (Ahmedabad) and Loba Chemie. Pvt. Ltd. (Mumbai). Melting points were determined by open tube capillary method and are uncorrected. Purity of compounds was checked by thin layer chromatography (TLC) on silica gel G in solvent system hexane-ethyl acetate (1:4), the spots were located under iodine vapours or UV light. IR spectra of all compounds were recorded on FT-IR 8400S Shimadzu spectrophotometer using KBr. Mass spectra were obtained using 2010EV LCMS Shimadzu instrument.

Scheme of Synthesis:



General Procedure of Preparation of 2-mercapto-6, 7-dimethoxyquinazolin-4(3H)-one (Jain *et al.,* 2010)

- Mixture of methyl 2-amino-4, 5-dimethoxybenzoate (2 gm, 0.0094 mol) and thiourea (1.42 gm, 0.0188 mol) was heated on sand bath at 175-180^{0}C for about 1 hour.
- When all melted mass converted to solid, it was dissolved in 20% NaOH solution and filtered to remove undissolved impurities, then cooled to 0-5^{0}C.
- The solution was acidified with conc. Hydrochloric acid. Precipitates obtained was filtered out and washed with ice-cold water and dried. The product was recrystallised from water. **(2)**

General procedure of Preparation of 6, 7-dimethoxy-2-(methylsulfanyl)-quinazolin-4(3H)-one (Jain *et al.,* 2010; Algarsamy *et al.,* 2007)

- The 2-mercapto-6, 7-dimethoxyquinazolin-4(3*H*) one (1.42 gm, 0.006mol) was dissolved in 20ml sodium hydroxide solution (20%), cooled to 0-5°C.
- To the above solution, Dimethyl sulphate (1.7 ml, 0.018mol) was added drop wise for half an hour with stirring. Again it was stirred for another 3-4 hours and placed in freezer for overnight. The solid separated out was filtered, washed with ice-cold water, dried and recrystallised from chloroform/ethanol (50:50). **(3)**

General Procedure of Preparation of 2-(4-substitutedphenylamino)-6,7-dimethoxyquinazolin-4(3H)-one

- 6,7-dimethoxy-2-(methylsulfanyl) quinazolin-4(3*H*)-one (1 gm, 0.004 mol) was dissolved in iso propyl alcohol in 250 ml round bottom flask and then p-substituted aniline (2.5 gm, 0.02 mol) was added.
- Reaction mixture was refluxed for 12 hrs. The reaction mixture was cooled and poured into ice water. The solid separated out was filtered, dried and recrystallised from ethanol. **(4a-4e)**

Physical Characteristics of Synthesized Compounds

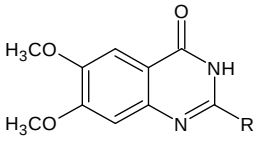


Table. 1: Mobile phase: (Hexane: Ethyl acetate 1:4)

Compound Code	R	Molecular Formula	Molecular Weight (g/mol)	Melting Point (^{o}C)	Yield (% w/w)	R_f Value
2	-SH	$C_{10}H_{10}N_2O_3S$	238.36	243-245	75	0.6
3	-SCH_3	$C_{11}H_{12}N_2O_3S$	252.29	231-232	40	0.4
4a	p-Flouro Anilinium	$C_{16}H_{14}N_3O_3F$	315	212-215	35	0.52
4b	p-Methyl Anilinium	$C_{17}H_{17}N_3O_3$	311	220-223	65	0.45
4c	p-Methoxy Anilinium	$C_{17}H_{17}N_3O_4$	327	206-209	61.5	0.49
4d	p-Chloro Anilinium	$C_{16}H_{14}N_3O_3Cl$	331	198-201	41.3	0.51
4e	p-Nitro Anilinium	$C_{16}H_{14}N_4O_5$	342	203-205	40	0.42

Spectral data of synthesized compounds

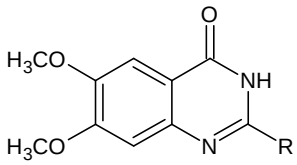


Table. 2:

Compound Code	R	IR (υ, cm^{-1})	Mass (m/z)	NMR (δ, ppm)
2	-SH	-NH (3259), -SH (2560), -C=O (1674), -C=N (1616), -C-O (1203)	238.3(M^+)	----
3	$-SCH_3$	-NH (3336), -C=O (1675), -C=N (1612),-C-O (1242)	252.4(M^+)	----
4a	p-Flouro Anilinium	-NH (3280), -C=O (1674), -C=N (1612), -C-O (1242), -C-F (1029)	315.4(M^+)	----
4b	p-Methyl Anilinium	-NH (3300), -C=O (1666), -C=N (1616), -C-O (1242)	311.9(M^+)	----
4c	p-Methoxy Anilinium	-NH (3306), -C=O (1674), -C=N (1612), -C-O (1242)	327.9(M^+)	----
4d	p-Chloro Anilinium	-NH (3363), -C=O (1662), -C=N (1612), -C-O (1242), -C-Cl (760)	331.7(M^+)	9.08 (s, 1H, N**H**), 6.45-7.41 (m, 6H, Ar**H**), 4.48 (s, 1H, N**H**), 3.35 (s, 6H, C$\mathbf{H_3}$)
4e	p-Nitro Anilinium	-NH (3400), -C=O (1674), -C=N (1608), -N-O (1546), -C-O (1242)	342.8(M^+)	9.0 (s, 1H, N**H**), 7.84-7.87 (d, 2H, Ar**H**), 7.24-7.29 (d, 2H, Ar**H**), 7.41 (s, 1H, Ar**H**), 6.85 (s, 1H, Ar**H**), 4.48 (s, 1H, N**H**), 3.35 (s, 6H, C$\mathbf{H_3}$)

Measurement of Antihypertensive Activity (α_1-Adrenergic Receptor Blocking Activity) (Vogel *et al.*, 2002; Kulkarni *et al.*, 2006)

Apparatus

Physiograph, Student organ bath, Haemostatic forceps, aeration tube cum tissue holder.

Procedure

- The assembly was set up and arrangements were made for experimental conditions mentioned above.
- The male rat was sacrificed
- The abdominal cavity was quickly opened and the testes and vas deferens were exposed.
- The vas deferens of the rat was easily identifiable as white thin tubular structures. Both have blood vessels running along their lengths and they emanate from the epididymis close to the testes.
- One of the vas deferens was cut free from the epididymis and dissected as close to the junction with the urethra as possible. It was cut at this point and transferred to a petri dish containing Kreb's solution maintained at 37^o C with aeration.
- All the connective tissue and the blood vessels were carefully removed. Adhere closely to the muscle and expel any semen from the vas deferens by gently pressing the tissue with a finger.
- The tissue was mounted in mammalian organ bath and connected to physio graph. The tissue was allowed to stabilize for half an hour. Once tissue was stabilized, graded doses of Adrenaline were added to obtain contractile responses. After each response wash was given with PSS.
- Contractions of the vas deferens induced by the α-adrenergic agonist after addition of the prazosin (Standard) as α-adrenergic antagonist were compared with the initial values and expressed as percentage thereof. An *IC*50 was calculated by linear regression analysis.
- This procedure was repeated for test compounds and *IC*50 value was calculated.
- Kreb's solution:

NaCl	5.9 gm/l
KCl	0.39 gm/l
$CaCl_2$	0.28 gm/l
KH_2PO_4	0.16 gm/l
$MgSO_4$	0.11 gm/l
Glucose	2.0 gm/l
$NaHCO_3$	2.1 gm/l

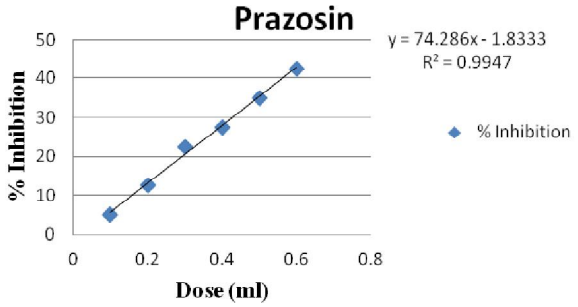


Fig. 1: % Inhibition vs dose curve of Prazosin.

y = 74.28x - 1.833

If y = 50%, then x = 0.7ml dose,

IC_{50} of Prazosin = dose for 50% inhibition* conc. ÷ bath capacity

= (0.7ml) × (1µg/ml) ÷ 25ml = 0.028µg/ml

Table. 3: α_1-Adrenergic Receptor Blocking Activity of Prazosin Calculation of *IC*50.

Compound	Dose (ml)	Control (cm) (H)	Test (cm) (h)	% Inhibition	IC_{50} (µg/ml)
Prazosin	0.1	4.0	3.8	5.00	0.028
	0.2	4.0	3.5	12.5	
	0.3	4.0	3.1	22.5	
	0.4	3.9	2.8	27.5	
	0.5	3.9	2.5	35.00	
	0.6	3.9	2.2	42.5	

Table. 4: Screening of α_1-Adrenergic Receptor Blocking Activity.

Compound code	Dose (ml)	Control (cm) (H)	Test (cm) (h)	% Inhibition	IC_{50} (µg/ml)
4a	0.1	3.9	3.7	5.12	0.4
	0.3	3.9	3.3	15.38	
	0.5	4.0	3.0	25	
4b	0.1	4.0	3.8	5	0.99
	0.3	4.0	3.6	10	
	0.5	3.9	3.4	12.5	
4c	0.1	3.9	3.8	2.56	0.63
	0.3	3.9	3.6	7.69	
	0.5	3.9	3.3	15.38	
4d	0.1	3.9	3.7	5.12	0. 65
	0.3	4.0	3.5	12.5	
	0.5	3.9	3.2	17.9	
4e	0.1	4.0	3.7	7.5	0.47
	0.3	4.0	3.4	15	
	0.5	3.9	3.0	23.07	

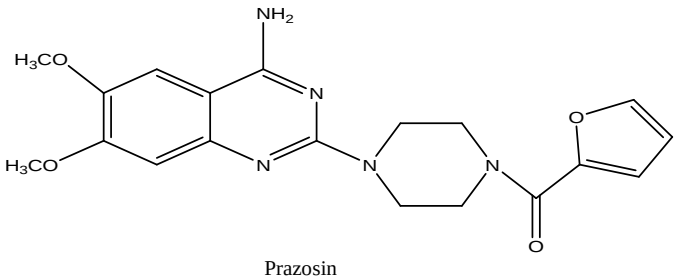
RESULT AND DISCUSSION

All synthesized compounds were screened for α_1 adrenergic receptor blocking activity. Prazosin was used as standard reference drug for α_1 adrenergic receptor blocker screening. All synthesized compound 4a, 4b, 4b, 4c and 4d show less activity as compared to standard prazosin.

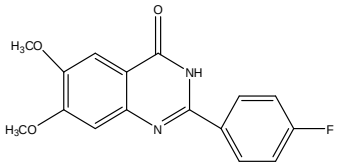
Table. 5: Result of α_1-Adrenergic Receptor Blocking Activity

.Compound code	IC_{50} (µg/ml)
4a	0.4
4b	0.99
4c	0.63
4d	0. 65
4e	0.47

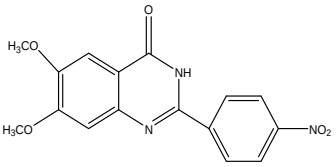
Compound **4a** and **4e** show better activity than other compounds in the series.



Prazosin



4a



4e

4a- 6,7-dimethoxy-2-(4-flourophenyl)quinazolin-4(3H)-one
4e- 6,7-dimethoxy-2-(4-nitrophenyl)quinazolin-4(3H)-one

CONCLUSION

All synthesized compounds (4a-4e) were characterized by IR, Mass, ^{1}H-NMR spectroscopy. All synthesized compounds were screened for α_1 adrenergic receptor blocking activity. Prazosin was used as standard reference drug for α_1 adrenergic receptor blocker screening. All synthesized compound 4a, 4b, 4b, 4c and 4d show less activity as compared to standard prazosin. Compound **4a** and **4e** show better activity than other compounds in the series. Synthetic point of view, compounds **4b** and **4c** were good in yield but compounds 4a, 4d, 4e were poor in yield.

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