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Synthesis and Antiinflammatory Activity of Some New Indolyl Substituted Quinazolin-4-(3*H*)-ones

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A series of 2-methyl-3-(2'-substituted indol-3'-yl)-substituted quinazolin-4(3*H*)-ones (**1-2**), 2-chloroacetylmethylene-3-(2'-substituted indol-3'-yl)-substituted quinazolin-4(3*H*)-ones (**3-4**), 2-hydrazinoacetylmethylene-3-(2'-substituted-indol-3'-yl)-substituted quinazolin-4(3*H*)-ones (**5-6**), 2-(substituted phenylmethyleneimino)aminoacetylmethylene-3-(2'-substituted indol-3'-yl)-substituted quinazolin-4(3*H*)-ones (**7-14**) and 2-(substituted phenylaminomethyleneacetyl-4'-oxo-3'-thiazalidinyl)-3-(2"-substituted indol-3"-yl)-substituted quinazolin-4(3*H*)-ones (**15-22**) have been synthesized. The compounds were screened for their antiinflammatory activity and were compared with the standard drug phenylbutazone. Out of these compounds the most active was 2-(*p*-chlorophenyl aminomethylacetyl-4'-oxo-1'-thiazolidinyl)-3-(indol-3"-yl)-6,8-dibromo quinazokin-4(3*H*)-one (**19**). The structures of these compounds have been confirmed by elemental and spectral analysis.

Key Words: Synthesis, Substituted Quinazolin-4-(3*H*)-ones, Antiinflammatory activity.

INTRODUCTION

Quinazolin-4(3*H*)-ones have been reported a variety of biological activities such as antibacteral[1,2], antifungal[3], anticonvulsant[4] and anti-inflammatory[5-8]. However the substitution pattern in the quinazolinone nucleus at 2/3 position by different heterocyclic moieties markedly modulates their antiinflammatory activity. Many indole[9-12] and thiazolidinone[13,14] derivatives have also been reported to possess potent antiinflammatory activity. Incorporating thus moieties in 2/3 position of quinazolinone nucleus might be thought to yield more potent antiinflammatory and substitution at 2/3 position further results in protection against inflammations. These findings prompted us to synthesize a new series of quinazolinones with a hope to get a better antiinflammatory activity.

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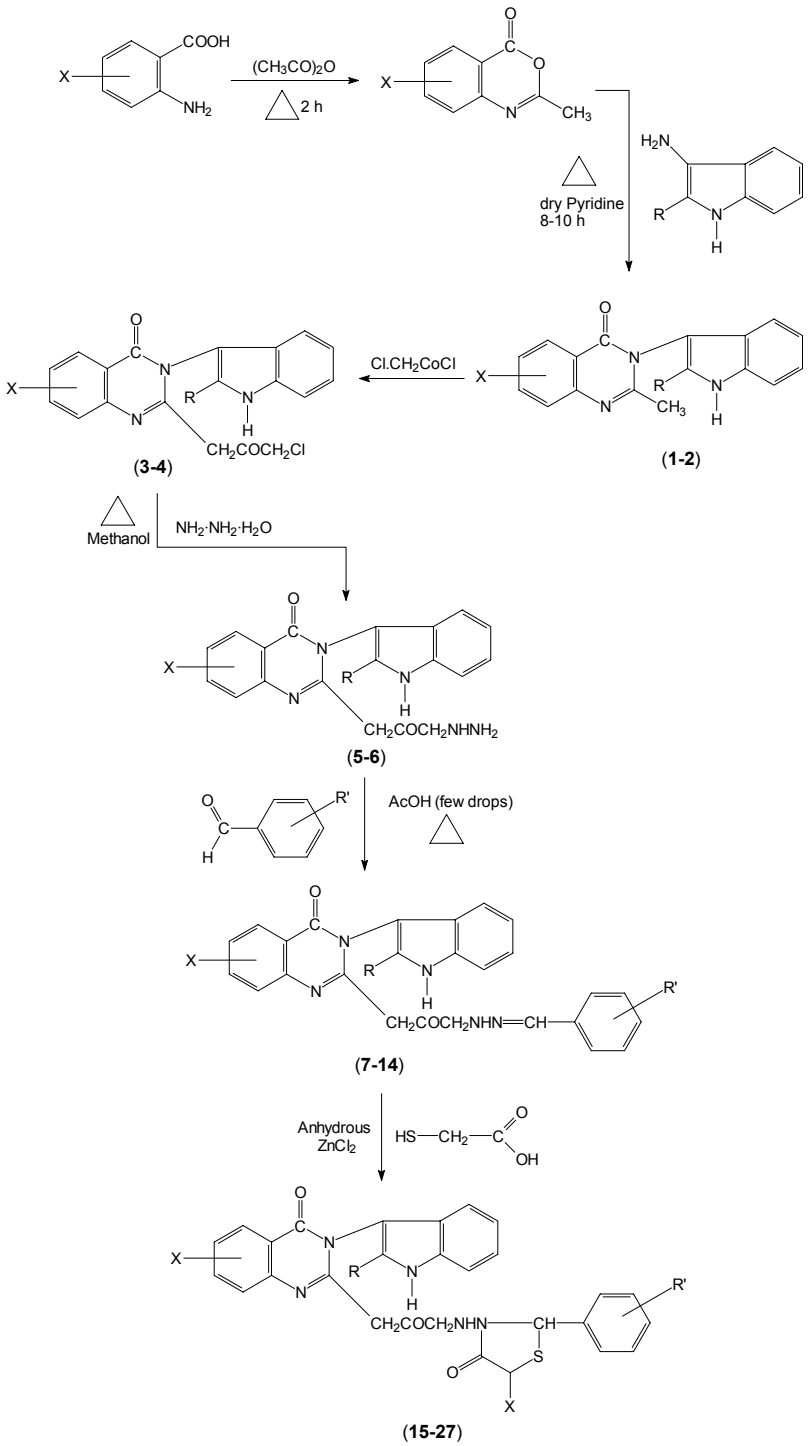
COOH
X
NH2
(CH3CO)2O
2 h
O
C
O
X
N
CH3
dry Pyridine
8-10 h
H2N
R
N
H
O
C
N
X
R
N
H
N
CH3
(1-2)
Cl.CH2CoCl
CH2COCH2Cl
(3-4)
Methanol
NH2·NH2·H2O
CH2COCH2NHNH2
(5-6)
R'
AcOH (few drops)
CH2COCH2NHN=CH
(7-14)
Anhydrous
ZnCl2
HS—CH2—C
OH
S
(15-27)

Scheme-I

The starting compound substituted anthranilic acid was prepared according to reported method by Wheeler *et al.*[15]. Compound 2-methyl-substituted benzoxazines was also synthesized by known method[16]. 2-Methyl-3-(2'-substituted indol-3'-yl-substituted quinazolin-4(3*H*)-ones (**1-2**), were prepared by the reaction of 2-methyl substituted benzoxazines with 2-substituted-3-aminoindoles in dry pyridine. On treatment with chloroacetyl chloride compounds (**1-2**) yielded the compounds (**3-4**). 2-hydrazinoacetyl methylene-3-(2'-substitutedindol-3'-yl)-substituted quinazolin-4(3H)-ones (**5-6**) were obtained by the reaction of compounds (**3-4**) with hydrazine hydrate. Furthermore reaction with substituted benzaldehyde in the presence of glacial acetic acid compounds (**5-6**) converted into 2-(substituted phenylmethyleneimino)aminoacetylmethylene-3-(2'-substituted indol-3'-yl)-substituted quinazolin-4(3*H*)-ones (**7-14**). Thioglycolic acid reacted with compound (**7-14**) in the presence of anhydrous $ZnCl_2$ to yield. 2-(Substituted phenylaminomethylacetyl{4'-oxo-3'-thiazolidinyl}-3-(2"-substituted indol-3"-yl)-substituted quinazolin-4(3*H*)-ones (**15-22**). The structures of all newly synthesized compounds were confirmed by spectral and analytical data.

EXPERIMENTAL

Melting points were determined in open capillaries and were uncorrected. The homogeneity of all compounds were checked by using silica gel-G plates. IR spectra were located in KBr on Beckman Acculab-10-spectrophotometer (ν_{max} in cm^{-1}) and ^1H NMR spectra in $CDCl_3$ on Bruker-400-FT and Bruker-300-FT instrument (chemical shift in δ ppm). Analysis (C,H,N) were within ± 0.4 % of theoretical values.

2-Methyl-3-(indol-3'-yl)-6-bromoquinazolin-4(3H) one (1): A mixture of 3-aminoindole (0.01 mol) and 6-bromo benzoxazone (0.02 mol) in dry pyridine (80 mL) was refluxed for 12 h. After refluxing, excess of solvent was removed and the residue neutralized with HCl. The solid separated out was washed with water and recrystallized from benzene to yield compound **1**. m.p. 210 ºC, yield 80 % molecular formula $C_{17}H_{12}N_3OBr$.

IR (KBr, ν_{max}, cm^{-1}): 3250 (NH), 1690 (C=0), 1605 (C=N), 570 (C-Br), 2960 (CH aliphatic). ^1H NMR ($CDCl_3$) δ in ppm: 7.90-8.50 (m, 8H, Ar-H), 8.95 (s, 1H, NH) 2.20 (s, 3H, CH_3).

Compound 2 was prepared using a similar procedure described for **1**. Physical data are given in Table-1.

2-Chloroacetylmethylene-3-(indol-3'-yl)-6-bromoquinazolin-4-(3*H*)-one (3): To a solution of 2-methyl-3-(indol-3'-yl)-6-bromoquinazolin-4-(3*H*)-one (**2**) (0.01 mol) in dry THF (100 mL) was added at 0 ºC temperature in chloroacetyl chloride drop by drop along with manual stirring for 5 h. The reaction mixture was further stirred for 6 h at room temperature.

TABLE-1
PHYSICAL† AND PHARMACOLOGICAL PROPERTIES OF COMPOUND **1-22**

Compd. no.	X	R	R^1	m.p. (ºC)	Yield (%)	Recrystallization solvent	m.f.	Antiinflammatory (%)*
1	6 Br	H	-	210	80	Benzene	$C_{17}H_{12}N_3OBr$	-
2	6,8-di Br	C_2H_5	-	260	75	Methanol	$C_{19}H_{15}N_3OBr_2$	-
3	6 Br	H	-	172	72	Methanol	$C_{19}H_{13}N_3O_2Br$	-
4	6,8-di Br	C_2H_5	-	240	70	Ethanol	$C_{21}H_{16}N_3O_2Br_2$	-
5	6 Br	H	-	220	75	Methanol	$C_{19}H_{16}N_5O_2Br$	-
6	6,8-di Br	C_2H_5	-	255	70	Acetic acid	$C_{21}H_{19}N_5O_2Br_2$	-
7	6 Br	H	4-Cl	180	62	Ethanol	$C_{26}H_{19}N_5O_2BrCl$	29.24
8	6 Br	H	4-OH	175	60	Methanol	$C_{26}H_{20}N_5O_3BrCl$	27.56
9	6 Br	H	4-OCH_3	190	60	Acetic acid	$C_{27}H_{22}N_5O_3BrCl$	28.44
10	6 Br	H	4-OCH_3	198	58	Ethanol	$C_{27}H_{22}N_5O_2Br$	26.18
11	6,8-di Br	C_2H_5	4-Cl	230	56	Benzene	$C_{28}H_{22}N_5O_2Br_2Cl$	34.32
12	6,8-di Br	C_2H_5	4-OH	225	62	Ethanol	$C_{28}H_{23}N_5O_3Br_2$	32.22
13	6,8-di Br	C_2H_5	4-OCH_3	218	60	Methanol	$C_{29}H_{25}N_5O_3Br_2$	33.68
14	6,8-di Br	C_2H_5	4-CH_3	208	55	Acetone	$C_{29}H_{25}N_5O_2Br_2$	30.48
15	6 Br	H	4-Cl	215	45	Benzene	$C_{28}H_{21}N_5O_3SBr_2$	36.18
16	6 Br	H	4-OH	220	52	Acetic acid	$C_{28}H_{22}N_5O_4SBr$	34.12
17	6 Br	H	4-OCH_3	140	48	Ethanol	$C_{29}H_{24}N_5O_4SBr$	35.44
18	6 Br	H	4-OCH_3	250	50	Acetone	$C_{29}H_{24}N_5O_3SBr$	32.56
19	6,8-di Br	C_2H_5	4-Cl	260	46	Methanol	$C_{30}H_{24}N_5O_3SBr_2Cl$	38.34
20	6,8-di Br	C_2H_5	4-OH	242	45	Benzene	$C_{30}H_{25}N_5O_4SBr_2$	35.82
21	6,8-di Br	C_2H_5	4-OCH_3	205	50	Ethanol	$C_{31}H_{27}N_5O_4SBr_2$	36.84
22	6,8-di Br	C_2H_5	4-CH_3	224	48	Benzene	$C_{31}H_{27}N_5O_3SBr_2$	34.89
	Phenylbutazane		–	–	–	–	–	37.22

†Elemental analysis for C, H, N was obtained for all compounds with ± 0.4 % of the theoretical values; *Dose 50 mg/kg p.o.

After stirring, excess of solvent was distilled off, cooled poured onto crushed ice and filtered. The solid thus obtained was recrystallized from methanol to yield 3. m.p. 172 ºC, yield 72 %, m.f. $C_{19}H_{13}N_3O_2BrCl$.

IR (KBr, ν_{max}, cm^{-1}): 3260 (NH), 2950 (CH-aliphatic), 1700 (C=O), 1595 (C=N), 580 (C-Br). ^{1}H NMR ($CDCl_3$) δ in ppm: 7.95-8.60 (m, 8H, Ar-H), 9.05 (s, 1H, NH), 3.95 (s, 2H, CH_2), 4.15 (s, 2H, CH_2Cl).

Compound 4 was prepared using a similar procedure described for 3 and physical data are given in Table-1.

2-(*p*-Chlorophenylmethylenimino)aminoacetylmethylene-3-(indol-3'-yl)-6-bromo-quinazolin-4-(3*H*)-one (7): A mixture of compound **5** (0.01 mol) and *p*-chlorobenzaldehydle (0.01 mol) in methanol (60 mL) was refluxed for 8 h in presence of glacial acetic acid (4 mL). The excess of solvent was distilled off and the residue thus obtained washed with diethyl either and recrystallized from ethanol to yield **7**. m.p. 180 ºC, yield 62 %, m.f. $C_{29}H_{19}N_5O_2BrCl$.

IR (KBr, ν_{max}, cm^{-1}): 3280 (NH), 1700 (C=O), 1590 (C=N), 2970 (CH aliphatic), 570 (C-Br). ^{1}H NMR ($CDCl_3$) δ in ppm: 7.80-8.60 (m, 12H, Ar-H), 9.05 (s, 1H, NH), 4.12 (d, 2H, CH_2NH), 3.90 (d, 2H, CH_2-CO), 5.65 (t, 1H, NH-N=CH), 6.05 (s, 1H, =CH-Ar).

All the compounds (**8-14**) of this step were prepared using a similar procedure described for **7** and physical data are given in Table-1.

2-(*p*-Chlorophenylaminomethylacetyl-4'-oxo-3'-thiazolidinyl)-3-(indol-3''-yl)-6-bromo quinazolin-4-(3*H*)-one (15): A mixture of compound **7** (0.01 mol) and thioglycolic acid (0.01 mol) in the presence of anhydrous $ZnCl_2$ and absolute ethanol (80 mL) was refluxed for 16 h. The solvent was removed under reduced pressure. The solid thus obtained was treated with saturated solution of $NaHNO_3$ and then washed with water, dried over anhydrous sodium sulphate. The product finally obtained was recrystallized from methanol to give **15**. Compound **19**: m.p. 215 ºC, yield 45 %, m.f. $C_{28}H_{21}N_5O_3BrCl$.

IR (KBr, ν_{max}, cm^{-1}): 3275 (NH), 1705 (C=O), 1600 (C=N), 2975 (CH aliphatic), 570 (C-Br), 690 (C-S-C). ^{1}HNMR ($CDCl_3$) δ in ppm: 7.15-8.50 (m, 12H, Ar-H), 9.15 (s, 1H, NH), 4.16 (s, 2H, CH_2NH), 3.85 (d, 2H, CH_2), 5.60 (t, 1H, NH-N), 6.12 (s, 1H, CH), 3.65 (s, 2H, CH_2 of β-thiolactam ring).

All the compounds (**16-22**) of this step were prepared using a procedure described for **15** and physical data are given in Table-1.

Antiinflammatory activity against carragunan induced hind paw oedema in rats was determined by the method of Winter *et al.*[17]. This study was conducted on albino rats of either sex (100-175 g). The rats were divided into groups of five animals each. Compounds were screened for anti-inflammatory activity at 50 mg/kg per oral. The percentage of antiinflammatory activity was calculated according to the following formula.

$$\text{Antiinflammatory activity (\%)} = 1 - \frac{V_t}{V_c} \times 100$$

where V_t and V_c are the volume of oedema in drug treated and control group, respectively. Phenylbutazone was used as a reference drug for comparative evaluation.

RESULTS AND DISCUSSION

Compound **7-22** have been tested for their antiinflammatory activity at the dose of 50 mg/kg p.o. of varying degree from 26.18 to 88.34 % and biological result are given in Table-1. Among these compounds, compound **19** found to possess most potent antiinflammatory activity than other compounds. Compound **7-14** exhibited mild to moderate antiinflammatory activity (26.18 to 34.32 %). The cyclization of these derivatives into their corresponding thiazolidinones (**15-22**) enhanced antiinflammatory activity (32.56 to 38.34 %). It is observed that compound (**10**) having *p*-methylphenyl group as substitutent showed least activity (26.18 %). While compound (**19**) substituted with 4-chlorophenyl ring exhibited the maximum activity (38.34 %). This compound showed better antiinflammatory activity (38.34 %) at the dose of 50 mg/kg p.o. than that of standard drug phenyl butazone (37.22 %).

REFERENCES

1. M.M. Gharab, Abdel, S.G. Hamide and A.E. El-Hakim, *Indian J. Heterocycl. Chem.*, **5**, 115 (1995).
2. P.S.N. Reddy, T.V. Vasantha and C.N. Raju, *Indian J. Chem.*, **38B**, 40 (1999).
3. P. Paneerseelvam, R.V.P. Chandran and S.K. Sridhar, *Indian J. Pharm. Sci.*, **65**, 268 (2003).
4. F.J. Wolfe, L.T. Ratham, M.C. Sleevi, J.A. Campbell and T.D. Greenwood. *J. Med. Chem.*, **33**, 161 (1990).
5. A. Kumar, R.S. Verma, B.P. Jaju and J.N. Sinha, *J. Indian Chem. Soc.*, **67**, 920 (1990).
6. J.S. Mohan and K.S. Manjunatha, *Indian J. Heterocycl. Chem.*, **8**, 115 (1998).
7. R. Tyagi, B. Goel, V.K. Srivastava and A. Kumar, *Chem. Abstr.*, **131**, 129966x (1999).
8. L.A. Lerry, J.B. Michael, B.J. Charles, E.G. Don and C.U. David, *Chem. Abstr.*, **135**, 196553t (2001).
9. R. Sharma, *Chem. Abstr.*, **136**, 134670d (2002).
10. V.N. Sonar, Y.S. Khadar and N. Sreenivasulu, *Indian J. Heterocycl. Chem.*, **10**, 299 (2001).
11. E. Bansal, V.K. Srivastava and A. Kumar, *Indian J. Chem.*, **39B**, 357 (2000).
12. Mohd. Amir, N. Dhar and S.K. Tiwari, *Indian J. Chem.*, **36B**, 96 (1997).
13. S. Mishra, S.K. Srivastava and S.D. Srivastava, *Indian J. Chem.*, **36B**, 826 (1997).
14. S.K. Srivastava, R. Yadav and S.D. Srivastava, *Indian J. Chem.*, **43B**, 399 (2004).
15. A.A. Wheeler and W.M. Dats, *J. Am. Chem. Soc.*, **32**, 770 (1910).
16. M.T. Bogert and H.A. Soil, *J. Am. Chem. Soc.*, **29**, 517 (1907).
17. C.A. Winter, E.A. Rislesy and G.W. Nuss, *Proc. Soc. Exp. Biol.*, **111**, 544 (1962).

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