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PHARMACOLOGICAL EVALUATION OF 3-ETHYL-2-SUBSTITUTEDAMINO-3H-QUINAZOLIN-4-ONES AS ANALGESIC AND ANTI-INFLAMMATORY AGENTS

R.V. Sheorey[1], A. Thangathiruppathy[2], V. Alagarsamy[3,*]
[1] Department of Pharmacy, Karpagam University, Eachanari Post, Coimbatore – 641 021, Tamilnadu State, India.
[2] Department of Pharmacology, SB College of Pharmacy, Sivakasi – 626 130, Tamilnadu State, India
[3] Medicinal Chemistry Research Laboratory, MNR College of Pharmacy, Sangareddy, Gr. Hyderabad -502 294, Andhra Pradesh State, India.
*Professor & Principal, MNR College of Pharmacy, Sangareddy, Gr. Hyderabad -502 294, Andhra Pradesh, India
E-mail: drvalagarsamy@gmail.com

Summary

A series of 3-ethyl-2-substituted amino-quinazolin-4(3*H*)-ones were synthesized by reacting the amino group of 3-ethyl-2-hydrazino quinazolin-4(3*H*)-one with a variety of aldehydes and ketones. The starting material 3-ethyl-2-hydrazino quinazolin-4(3*H*)-one was synthesized from ethylamine. The title compounds were investigated for analgesic, anti-inflammatory activities. The compound 2-(1-ethylpropylidene-hydrazino)-3-ethyl-quinazolin-4(3*H*)-one **(S2)** emerged as the most active compound of the series and it is moderately more potent in its analgesic and anti-inflammatory activities when compared to the reference standard diclofenac sodium.

Keywords: Quinazoline, analgesic, anti-inflammatory activity

Introduction

Nonsteroidal anti-inflammatory drugs (NSAIDs) are commonly prescribed for the treatment of acute and chronic inflammation, pain, and fever. The most of NSAIDs act via inhibition of cyclooxygenase, thus preventing prostaglandin biosynthesis. However, this mechanism of action is also responsible for their main undesirable effects, gastrointestinal (GI) ulceration and, less frequently, nephrotoxicity. The increase in hospitalization and deaths due to GI-related disorders parallels the increased use of NSAIDs. Therefore, the discovery of new safer anti-inflammatory drugs represents a challenging goal for such a research area[1, 2, 3, 4].

On our going medicinal chemistry research - program we found that quinazolines and condensed quinazolines exhibit potent central nervous system (CNS) activities including analgesic, anti-inflammatory and anticonvulsant behavior[5,6]. Quinazolin-4(3*H*)-ones with 2,3-substitution are reported to posess significant analgesic, anti-inflammatory[7,8] and anticonvulsant activities[9]. Earlier we have documented some lead 2-phenyl-3-substituted quinazolines[10] (Figure 1, I), 2-methyl-3-substituted quinazolines[11] (Figure 1, II), 2-methylthio-3-substituted quinazaolines[12] (Figure 1, III), and 2,3-disubstituted quinazolines[13] that exhibited good analgesic and anti-inflammatory properties. The present work is an extension of our ongoing efforts towards the development and identification of new molecules for analgesic and anti-inflammatory activities. With this background in the present study we have synthesized a series of 3-ethyl-2-substitutedamino-quinazolin-4(3*H*)-ones. The synthesized compounds were tested for their analgesic and anti-inflammatory activities.

see Fig. 1

Experimental design

Chemistry

Melting points (mp) were taken in open capillaries on a Thomas Hoover melting point apparatus and are uncorrected. IR spectra of the synthesized compounds were recorded by FT-IR (Shimadzu, Japan) using KBR pellet (υ max in cm^{-1}). The NMR spectra of the synthesized compounds were recorded in $CDCl_3$ (unless specified) with TMS as internal reference (chemical shift in δ, ppm) using Varian 300 MHz and Bruker 500 MHz (Washington, USA) spectrometers. The Mass spectra of the compounds were obtained on JEOL GC mate instrument (Masspec, Japan). Elemental analyses were performed in Perkin-Elmer 2400 CHN elemental analyzer (Waltham, USA). The progress of the reaction was monitored on readymade silica gel plates (Merck) using chloroform: methanol (9:1) as a solvent system. Iodine was used as a developing agent. Spectral data (IR, NMR and mass spectra) confirmed the structures of the synthesized compounds and the purity of these compounds was ascertained by microanalysis. Elemental (C, H, N) analyses indicated that the calculated and observed values were within the acceptable limits (± 0.4%). All chemicals and reagents were obtained from Aldrich (USA), Lancaster (UK) or Spectrochem Pvt. Ltd (India) and were used without further purification.

Synthesis of Ethyl-2-thioxo-2,3-dihydro-1H-quinazolin-4-one (4)

A solution of Ethylamine (1.31 g; 0.02 mol) in dimethyl sulfoxide (10 mL) was stirred vigorously. To this was added carbon disulphide (1.6 mL) and aqueous sodium hydroxide (1.2ml of 20 molar solution) dropwise during 30 min with stirring. Dimethyl sulphate (2.5g; 0.02 mol) was then added gradually keeping the reaction mixture in freezing mixture with stirring and the stirring was continued for further 2 h. The reaction mixture was then poured into ice-water and the solid obtained was filtered, washed with water, dried and recrystallized from ethanol.

Methyl anthranilate (**3**) (1.5 g; 0.01 mol) and the above prepared *N*-(ethyl) methyl dithiocarbamic acid (0.01 mol), were dissolved in ethanol (20 mL). To this anhydrous potassium carbonate (100 mg) was added and refluxed for 23 h. The reaction

mixture was cooled in ice and the solid separated was filtered and purified by dissolving in 10% alcoholic sodium hydroxide solution and reprecipitating by the treatment with dilute hydrocholoric acid. The solid obtained was filtered, washed with water, and dried. It was recrystallized from ethanol to afford **(4).**

Yield = 85 %, mp 290-291°C; IR (KBr) cm^{-1}: 3250 (NH), 1668 (C=O), 1220 (C=S); ^1H NMR ($CDCl_3$) δ: 0.95-1.05 (t, 3H, $CH_2C\underline{H}_3$),1.39-1.50 (q, 2H, $C\underline{H}_2CH_3$), 7.10-7.50 (m, 4H, ArH), 10.55 (br s, 1H, NH, D_2O Exchangeable); MS (m/z): 206 (M^+); *Anal.* Calcd. for $C_{10}H_{10}N_2OS$: C, 58.22; H, 4.88; N, 13.58. Found: C, 58.25; H, 4.90; N, 13.63.

Synthesis of 3-Ethyl-2-methylsulfanyl-3H-quinazolin-4-one (5)

The 3-ethyl-2-thioxo-2,3-dihydro-1*H*-quinazolin-4-one (**4**) (0.01 mol) was dissolved in 40 mL of 2% alcoholic sodium hydroxide solution. To this dimethyl sulfate (0.01 mol) was added drop wise with stirring. The stirring was continued for 1 h, the reaction mixture was then poured into ice water. The solid obtained was filtered, washed with water, dried and recrystallized from ethanol.

Yield = 86%, mp 173-174 °C; IR (KBr) cm^{-1}: 1680 (C=O), 1605 (C=N); ^1H NMR ($CDCl_3$) δ: 0.90-1.10 (t, 3H, $CH_2C\underline{H}_3$), 1.35-1.52 (q, 2H, $C\underline{H}_2CH_3$), 2.70 (s, 3H, SCH_3), 7.20-7.60 (m, 4H ArH); MS (m/z): 220 (M^+); *Anal.* Calcd for $C_{11}H_{12}N_2OS$: C, 59.97; H, 5.49; N, 12.71. Found: C, 59.92; H, 5.51; N, 12.74.

Synthesis of 3-Ethyl-2-hydrazino--3H-quinazolin-4-one (6)

The 3-ethyl-2-methylsulfanyl-3*H*-quinazolin-4-one (5) (0.01 mol) was dissolved in ethanol (25 mL). To this hydrazine hydrate (99%) (0.01 mol) and anhydrous potassium carbonate (100 mg) was added and refluxed for 28 h. The reaction mixture was cooled and poured into ice-water. The solid so obtained was filtered, washed with water, dried and recrystallized from chloroform: benzene (25:75) mixture.

Yield = 80%, mp 193-195 °C; IR (KBr) cm^{-1}: 3330, 3205 (NH NH_2), 1670 (C=O), 1610 (C=N); ^1H NMR ($CDCl_3$): δ 0.91-1.00 (t, 3H, $CH_2C\underline{H}_3$), 1.30-1.48 (q, 2H, $C\underline{H}_2CH_3$), 4.56 (br s, 2H, NH_2 D_2O Exchangeable), 7.15-7.30 (m, 4H, ArH), 10.31 (br s, 1H, NH D_2O Exchangeable); MS (m/z): 204 (M^+); *Anal.* Calcd for $C_{10}H_{12}N_4O$: C, 58.81; H, 5.92; N, 27.43. Found: C, 58.85; H, 5.90; N, 27.41.

Synthesis of 3-Ethyl-2-(1-methylpropylidene-hydrazino)-3H-quinazolin-4-one (S1)

A mixture of 3-ethyl-2-hydrazino-3*H*-quinazolin-4-one **(6)** (0.004 mol) and ethyl methyl ketone (0.004 mol) in glacial acetic acid was refluxed for 33 h. The reaction mixture was poured into ice water. The solid obtained was recrystallized from ethanol.

Yield = 73%, mp 205-206 C; IR (KBr) cm^{-1}: 3260 (NH), 1680 (C=O), 1608 (C=N); ^1H-NMR ($CDCl_3$): δ 1.35-1.50 (t, 3H, $CH_2C\underline{H}_3$), 1.70-1.81 (t, 3H, $CH_2C\underline{H}_3$) 2.35 (s, 3H, CH_3), 2.61-2.73 (q, 2H, $C\underline{H}_2CH_3$), 2.72-2.86 (q, 2H, $C\underline{H}_2CH_3$), 8.23-8.68 (m, 4H, ArH), 9.61 (br s, 1H, NH, D_2O Exchangeable); MS (m/z): 258 (M^+); *Anal.* Calcd. for $C_{14}H_{18}N_4O$: C, 65.09; H, 7.02; N, 21.68. Found: C, 65.03; H, 7.05; N, 21.69.

Synthesis of 3-Ethyl-2-(1-Ethyl propylidene-hydrazino)-3H-quinazolin-4-one (S2)

A mixture of 3-ethyl-2-hydrazino-3*H*-quinazolin-4-one **(6)** (0.004 mol) and diethyl ketone (0.004 mol) in glacial acetic acid was refluxed for 34 h. The reaction mixture was poured into ice water. The solid obtained was recrystallized from ethanol.

Yield = 79 %, mp 236-237 °C; IR (KBr) cm^{-1} : 3245 (NH), 1665 (C=O), 1605 (C=N); ^1H-NMR ($CDCl_3$) : δ 1.15-1.17 (t, 3H, $CH_2C\underline{H}_3$), 1.26-1.34 (m, 6H, $(CH_2C\underline{H}_3)_2$), 1.60-1.66 (m, 4H, $(C\underline{H}_2CH_3)_2$), 2.79-2.90 (q, 2H, $C\underline{H}_2CH_3$), 7.38-7.69 (m, 4H, ArH), 9.03 (br s, 1H, NH, D_2O Exchangeable); MS (m/z): 272 (M^+); *Anal.* Calcd. for $C_{15}H_{20}N_4O$: C, 66.15; H, 7.40; N, 20.57. Found: C, 66.19; H, 7.43; N, 20.55.

Synthesis of 3-Ethyl-2-(N-1-Phenylethylidene-hydrazino)-3H-quinazolin-4-one (S3)

A mixture of 3-ethyl-2-hydrazino-3*H*-quinazolin-4-one **(6)** (0.004 mol) and acetophenone (0.004 mol) in glacial acetic acid was refluxed for 30 h. The reaction mixture was poured into ice water. The solid obtained was recrystallized from ethanol. Yield = 74 %, mp 240-241 °C; IR (KBr) cm^{-1} : 3300 (NH), 1670 (C=O), 1605 (C=N); ^{1}H-NMR ($CDCl_3$): δ 0.95-1.08 (t, 3H, $CH_2C\underline{H}_3$), 1.32-1.41 (q, 2H, $C\underline{H}_2CH_3$) 1.94 (s, 3H, CH_3), 7.62-8.73 (m, 9H, ArH), 8.83 (br s, 1H, NH, D_2O Exchangeable); MS (m/z): 306 (M^+); *Anal.* Calcd. for $C_{18}H_{18}N_4O$: C, 70.56; H, 5.92; N, 18.28. Found: C, 70.51; H, 5.93; N, 18.25.

Synthesis of 3-Ethyl-2-(benzylidene-hydrazino)-3H-quinazolin-4-one (S4)

A mixture of 3-ethyl-2-hydrazino-3*H*-quinazolin-4-one **(6)** (0.004 mol) and benzaldehyde (0.004 mol) in glacial acetic acid was refluxed for 30 h. The reaction mixture was poured into ice water. The solid obtained was recrystallized from ethanol. Yield = 71 %, mp 231-233 °C; IR (KBr) cm^{-1}: 3280 (NH), 1685 (C=O), 1612 (C=N); ^{1}H-NMR ($CDCl_3$): δ 1.23-1.31 (t, 3H, $CH_2C\underline{H}_3$), 1.51-1.65 (q, 2H, $C\underline{H}_2CH_3$), 6.01 (s, 1H, CH), 7.32-8.41 (m, 9H, ArH), 9.06 (br s, 1H, NH, D_2O Exchangeable); MS (m/z): 292 (M^+); *Anal.* Calcd. for $C_{17}H_{16}N_4O$: C, 69.84; 5.51, 19.16. Found: C, 69.78; H, 5.53; N, 19.18.

Synthesis of 3-Ethyl-2-(N-(4-chloro-benzylidene-hydrazino)-3H-quinazolin-4-one (S5)

A mixture of 3-ethyl-2-hydrazino-3*H*-quinazolin-4-one **(6)** (0.004 mol) and 4-chloro benzaldehyde (0.004 mol) in glacial acetic acid was refluxed for 34 h. The reaction mixture was poured into ice water. The solid obtained was recrystallized from ethanol. Yield = 73 % yield, mp 256-258 °C; IR (KBr) cm^{-1}: 3310 (NH), 1685 (C=O), 1616 (C=N); ^{1}H-NMR ($CDCl_3$): δ 1.31-1.43 (t, 3H, $CH_2C\underline{H}_3$), 1.85-1.93 (q, 2H, $C\underline{H}_2CH_3$), 6.11 (s, 1H, CH), 7.82-8.73 (m, 8H, ArH), 9.38 (br s, 1H, NH, D_2O Exchangeable); MS (m/z): 327 (M^+); *Anal.* Calcd. for $C_{17}H_{15}N_4OCl$: C, 62.48; H, 4.62; N, 17.14. Found: C, 62.42; H, 4.65; N, 17.13.

Pharmacology

The synthesized compounds were evaluated for analgesic and anti-inflammatory activities. Student t-test was performed to ascertain the significance of all the exhibited activities. The test compounds and the standard drugs were administered in the form of a suspension (1% W/V carboxy methyl cellulose as a vehicle) by oral route. Each group consisted of six animals. The animals were maintained in colony cages at 25±2C, relative humidity of 45-55%, under a 12 h light and dark cycle; they were fed standard animal feed. All the animals were acclimatized for a week before use. The Institutional Animal Ethics committee approved the protocol adopted for the experimentation of animals[14].

Analgesic activity

Test for analgesic activity was performed by tail-flick technique[15,16] using swiss albino mice (25-35 g) of either sex selected by random sampling technique. Diclofenac sodium at a dose level of 5 mg/kg, 10 mg/kg and 20 mg/kg was administered orally as reference drug for comparison. The test compounds at three dose levels (5, 10, 20 mg/kg) were administered orally. The reaction time was recorded at 30 min, 1, 2 and 3h after the treatment, and cut-off time was 10 sec. The percent analgesic activity (PAA) was calculated by the following formula,

$$PAA = \left[\frac{T_2 - T_1}{10 - T_1}\right] X\ 100$$

where T_1 is the reaction time (s) before treatment, and T_2 is the reaction time (s) after treatment.

Anti-inflammatory activity

Anti-inflammatory activity was evaluated by carrageenan-induced paw edema test in rats[17]. Diclofenac sodium 5, 10 and 20 mg/kg was administered as a standard drug for comparison. The test compounds were administered at three dose levels (5, 10 and 20 mg/kg). The paw volumes were measured using the mercury displacement technique with the help of a plethysmograph immediately before and 30 min, 1, 2 and 3 h after carrageenan injection. The percent inhibition of paw edema was calculated using the following formula

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Percent inhibition I = 100[1- (a-x)/ (b-y)]
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Where **x** is the mean paw volume of rats before the administration of carrageenan and test compounds or reference compound (test group), **a** is the mean paw volume of rats after the administration of carrageenan in the test group (drug treated), **b** is the mean paw volume of rats after the administration of carrageenan in the control group, **y** is the mean paw volume of rats before the administration of carrageenan in the control group.

Statistical analysis

Statistical analysis of the biological activity of the synthesized compounds on animals was evaluated using a one-way analysis of variance (ANOVA). In all cases, post-hoc comparisons of the means of individual groups were performed using Tukey's test. A significance level of $P < 0.05$ denoted significance in all cases. All values are expressed as mean±SD (standard deviations). For statistical analysis we have used GraphPad Prism 3.0 version. (GraphPad Prism 3.0 version, GraphPad Software, Inc.11452 El Camino Real, #215, San Diego, CA 92130 USA).

Result and Discussion

The key intermediate 3-ethyl-2-thioxo-2,3-dihydro-1*H*-quinazolin-4-one **4** was prepared by reacting ethyl amine (**1**) with carbon disulphide and sodium hydroxide in dimethyl sulphoxide to give sodium dithiocarbamate, which was methylated with dimethyl sulfate to afford the dithiocarbamic acid methyl ester **(2)**. Compound **2** on reflux with methyl anthranilate **(3)** in ethanol yielded the desired 3-ethyl-2-thioxo-2,3-dihydro-1*H*-quinazolin-4-one **(4)** via the thiourea intermediate in good yield (85%). It was confirmed by IR spectra of compound **4** show intense peaks at 3250 cm^{-1} for cyclic thio urea (NH), 1668 cm^{-1} for carbonyl (C=O) and 1220 cm^{-1} for thioxo (C=S) stretching. ^1H NMR spectra of **4** showed multiplet around δ 1.02 – 2.05 and 7.10-7.50 for ethyl (5H) protons and aromatic (4H) protons respectively; and a singlet at δ 10.55 indicating the presence of NH. Data from the elemental analyses have been found to be in conformity with the assigned structure. Further the molecular ion recorded in the mass spectra is also in agreement with the molecular weight of the compound.

The 3-ethyl-2-methysulfanyl-3*H*-quinazolin-4-one **5** was obtained by dissolving **4** in 2% alcoholic sodium hydroxide solution and methylating with dimethyl sulfate with stirring at room temperature. The IR spectra of compound **5** showed disappearance of NH and C=S stretching signals of cyclic thiourea. It showed a peak for carbonyl (C=O) stretching at 1680 cm^{-1}. The ^1H NMR spectra of compound **5** showed singlets due to SCH_3, at δ 2.70, multiplet around 7.20-7.60 for aromatic (4H) protons respectively. Data from the elemental analyses and molecular ion recorded in the mass spectra further confirmed the assigned structure.

Nucleophilic displacement of methylthio group of **5** with hydrazine hydrate was carried out using ethanol as solvent to afford 3-ethyl-2-hydrazino-3*H*-quinazolin-4-one **6**. The long duration of reaction (28 h) required might be due to the presence of ethyl group at position **3**. The formation of **6** was confirmed by the ^1H NMR spectra showed singlets at δ 4.56 and 10.31 due to NH_2 and NH respectively, a multiplet at δ 1-1.5 and 7.15-7.30 for ethyl (5H) protons and aromatic (4H) protons respectively. The NH and NH_2 signals at 3330, 3205 cm^{-1} are appeared in the IR spectra. It also showed a peak

for carbonyl (C=O) at 1670 cm^{-1}. Data from the elemental analyses have been found to be in conformity with the assigned structure. Further the molecular ion recorded in the mass spectra is also in agreement with the molecular weight of the compound.

see Scheme 1.

The title compounds 3-ethyl-2-substituted amino-3*H*-quinazolin-4-ones **S1-S5** were obtained by the condensation of amino group of 3-ethyl-2-hydrazino-3*H*-quinazolin-4-one **(6)** with a variety of aldehydes and ketones. The formation of title product is indicated by the disappearance of peak due to NH_2 of the starting material in IR and ^1H NMR spectrum of all the compounds **S1-S5**. The IR ^1H NMR spectra of these compounds showed the presence of peaks due to ($N=CR_1R_2$) carbonyl (C=O), NH and Aryl groups. The mass spectra of the title compounds showed molecular ion peaks corresponding to their molecular formula. In mass spectra of compounds **S1-S5** a common peak at m/z 144 corresponding to quinazolin-4-one moiety appeared. The M^++2 peaks was observed in the spectra of compound **AS5** confirming the presence of a chlorine atom in the compounds. The relative intensities of these M^++2 peaks in comparison with M^+ peaks were in the ratio of 1:3. Elemental (C, H, N) analysis satisfactorily confirmed elemental composition and purity of the synthesized compounds.

Evaluation of analgesic activity was performed by the tail-flick technique (Kulkarni, 1980; Amour et al., 1940) using swiss albino mice. The results of analgesic testing indicate that the test compounds exhibited moderate analgesic activity at 30 min of reaction time and an increase in activity at 1 h which reached a peak level at 2 h. Decline in activity was observed at 3 h (Table 1). Compound **S1** with 1-methylpropylidene substituent showed good activity; with the increased lipophilicity (1-ethylpropylidene group, compound **S2)** showed increase in activity. Replacement of an alkyl chain at the C-2 position with a aralkyl group (compounds **S3**) leads to moderate decrease in activity. Placement of aryl group (compounds **S4)** also results in decreasing activity. Placement of aryl group with electron withdrawing substituent (compounds **S5**) leads to further decrease of activity. Compound 2-(1-ethylpropylidene-hydrazino)-3-ethyl-quinazolin-4(3*H*)-one **(S2)** emerged as the most active analgesic agent and it is moderately more potent when compared to the reference standard diclofenac sodium.

Anti-inflammatory activity was evaluated by the carragenenan-induced paw edema test in rats (Winter et al., 1962). The anti-inflammatory activity data (Table 2) indicated that all the test compounds protected rats from carrageenan-induced inflammation moderately at 30 min of reaction time with increased activity at 1 h that reached a peak level at 2 h. Decline in activity was observed at 3 h. The compound 2-(1-ethylpropylidene-hydrazino)-3-ethyl-quinazolin-4(3*H*)-one **(S2)** emerged as the most active analgesic agent and it is more potent when compared to the reference standard diclofenac sodium.

Conclusion

In our earlier studies, we observed that the presence of alkyl groups exhibited more analgesic and anti-inflammatory activities over aryl groups at the N-3 position. Hence in the C-2 position also we made a substitution in such a way to increase lipophilicity of the molecule. The placement of such a group enhanced the analgesic and anti-inflammatory activities. With this background, synthesis of new series of 3-ethyl-2-substituted amino-quinazolin-4(3*H*)-ones (**S1–S5**) have been described. The title compounds have exhibited promising analgesic and anti-inflammatory activities when tested by using the model tail-flick technique on swiss albino mice and carragenenan-induced paw edema test in rats respectively. Among the series, compound 2-(1-ethylpropylidene-hydrazino)-3-ethyl-quinazolin-4(3*H*)-one **(S2)** was found to be the most active compound of the series and it is moderately more potent in its analgesic and anti-inflammatory activities when compared to the

reference standard diclofenac sodium. Hence this compound could therefore serve as a lead molecule for further modification to obtain a clinically useful novel class of analgesic and anti-inflammatory agents.

see Table 1.

see Table 2.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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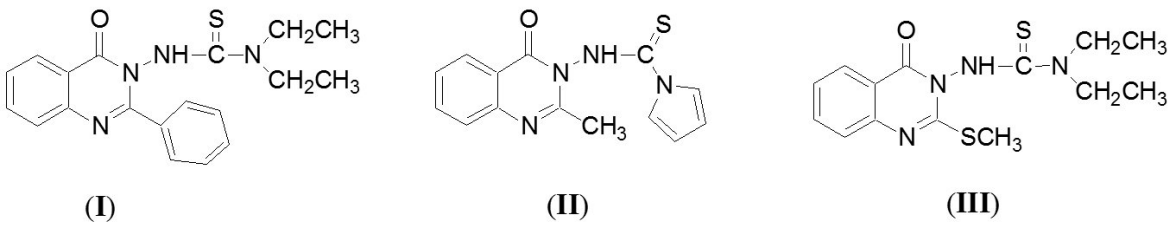
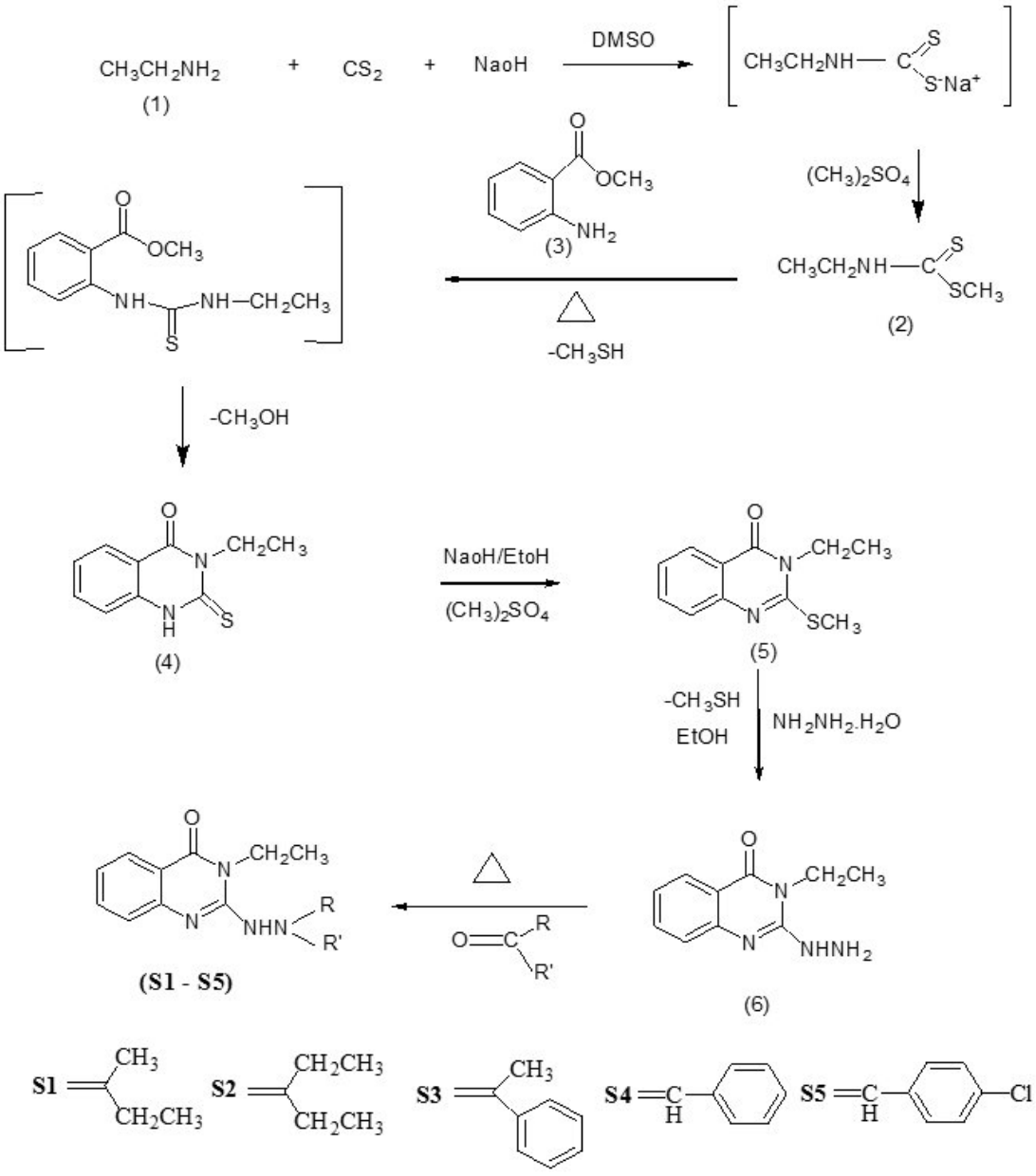


(I) **(II)** **(III)**

Figure 1. Lead molecules of quinazolin-4-ones



Scheme 1. Synthesis of 3-ethyl-2-substituted amino-3*H*-quinazolin-4-ones

Compound Code	Dose (mg/kg)	Percent Analgesic activity			
		30 min	1 h	2 h	3h
S1	5	25.93 ± 3.58^{c}	29.63 ± 4.58^{c}	33.80 ± 5.54^{c}	19.91 ± 2.39^{b}
	10	37.96 ± 3.54^{c}	43.98 ± 3.66^{c}	50.00 ± 3.53^{c}	31.94 ± 2.32^{c}
	20	49.07 ± 1.70^{c}	56.71 ± 2.74^{c}	62.73 ± 4.62^{c}	38.89 ± 3.10^{c}
S2	5	23.84 ± 2.59^{c}	27.55 ± 3.05^{c}	33.10 ± 3.43^{c}	21.53 ± 3.44^{c}
	10	42.13 ± 2.88^{c}	48.15 ± 1.17^{c}	55.09 ± 2.50^{c}	30.32 ± 4.74^{c}
	20	51.16 ± 4.04^{c}	59.26 ± 2.17^{c}	65.51 ± 3.19^{c}	40.97 ± 2.93^{c}
S3	5	23.38 ± 2.74^{c}	27.31 ± 3.77^{c}	33.33 ± 4.70^{c}	19.44 ± 3.92^{b}
	10	36.81 ± 3.30^{c}	42.82 ± 4.09^{c}	49.07 ± 3.35^{c}	26.39 ± 4.77^{c}
	20	45.14 ± 3.43^{c}	54.63 ± 4.17^{c}	60.41 ± 5.47^{c}	39.12 ± 3.69^{c}
S4	5	24.07 ± 3.28^{c}	29.86 ± 3.94^{c}	36.11 ± 3.34^{c}	15.51 ± 5.60^{a}
	10	38.89 ± 3.97^{c}	44.91 ± 2.50^{c}	49.07 ± 3.35^{c}	30.79 ± 3.03^{c}
	20	46.76 ± 3.05^{c}	52.78 ± 4.25^{c}	61.11 ± 2.32^{c}	40.74 ± 5.99^{c}
S5	5	18.52 ± 2.90^{c}	24.54 ± 3.26^{c}	28.47 ± 2.26^{c}	16.44 ± 2.71^{c}
	10	30.56 ± 2.56^{c}	34.72 ± 2.06^{c}	44.91 ± 4.08^{c}	28.70 ± 2.81^{c}
	20	40.74 ± 3.89^{c}	48.84 ± 4.04^{c}	52.78 ± 4.25^{c}	38.89 ± 2.32^{c}
Control		1.852 ± 1.85^{Ns}	5.787 ± 2.59^{Ns}	7.870 ± 2.50^{Ns}	3.935 ± 2.49^{Ns}
Std	5	21.76 ± 2.20^{c}	31.48 ± 2.62^{c}	35.42 ± 4.41^{c}	17.59 ± 2.52^{b}
	10	35.18 ± 3.89^{c}	42.82 ± 5.20^{c}	48.61 ± 5.83^{c}	29.17 ± 3.42^{c}
	20	48.15 ± 4.47^{c}	58.33 ± 4.40^{c}	62.04 ± 3.54^{c}	37.96 ± 3.54^{c}

Table 1. Analgesic activity of synthesized compounds (S1-S5)

Data expressed as mean SEM from six different experiments done in duplicate. Significance levels ^{a}p<0.05.; ^{b}p<0.01and ^{c}p<0.001 as compared with the respective control.

Compound Code	Dose (mg/kg)	Percent Protection			
		30 min	1 h	2 h	3h
S1	5	21.05 ± 5.43[c]	30.95 ± 3.78[c]	36.00 ± 1.33[c]	23.68 ± 1.73[c]
	10	40.35 ± 9.18[c]	48.81 ± 7.08[c]	51.55 ± 4.19[c]	40.06 ± 3.15[c]
	20	42.10 ± 10.87[c]	56.34 ± 7.18[c]	64.89 ± 4.22[c]	41.81 ± 2.78[c]
S2	5	33.33 ± 7.14[c]	35.71 ± 5.21[c]	40.00 ± 3.47[c]	28.07 ± 1.48[c]
	10	42.10 ± 1.92[c]	50.00 ± 4.91[c]	52.00 ± 2.48[c]	40.34 ± 2.76[c]
	20	47.36 ± 11.77[c]	59.52 ± 5.28[c]	66.66 ± 2.96[c]	45.61 ± 0.84[c]
S3	5	15.78 ± 5.25[a]	26.02 ± 6.66[c]	30.66 ± 2.20[c]	19.29 ± 1.15[a]
	10	31.57 ± 5.43[c]	38.09 ± 3.30[c]	42.67 ± 2.09[c]	30.70 ± 3.16[c]
	20	45.61 ± 11.98[c]	50.00 ± 6.50[c]	56.89 ± 4.18[c]	41.81 ± 5.13[c]
S4	5	21.05 ± 7.19[b]	26.19 ± 2.38[c]	29.33 ± 1.53[c]	18.42 ± 1.28[b]
	10	29.82 ± 6.47[c]	32.54 ± 4.62[c]	40.89 ± 3.55[c]	30.40 ± 3.08[c]
	20	40.35 ± 5.71[c]	42.06 ± 5.41[c]	48.66 ± 4.53[c]	32.16 ± 4.54[c]
S5	5	17.54 ± 6.17[b]	23.80 ± 4.07[c]	29.33 ± 0.973[c]	18.42 ± 1.33[b]
	10	24.56 ± 7.88[a]	30.15 ± 5.72[b]	38.22 ± 3.43[c]	22.51 ± 2.96[a]
	20	26.31 ± 7.31[a]	38.09 ± 5.99[c]	42.66 ± 5.53[c]	29.82 ± 3.26[b]
Std	5	16.66 ± 4.38[a]	24.20 ± 5.47[b]	30.66 ± 4.68[c]	20.17 ± 1.82[b]
	10	32.45 ± 9.83[b]	36.50 ± 4.33[c]	43.78 ± 3.69[c]	33.04 ± 2.97[b]
	20	41.22 ± 8.74[c]	54.36 ± 6.06[c]	65.11 ± 4.49[c]	47.22 ± 8.06[c]

Table 2. Anti-inflammatory activity of synthesized compounds (S1-S5)

Data expressed as mean SEM from six different experiments done in duplicate.
1Significance levels [a]p<0.05.; [b]p<0.01and [c]p<0.001 as compared with the respective control