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Anti-inflammatory, analgesic and antitubercular activity of 4,6-diphenyl-4,5,6, 7-tetrahydro-3-selena-1,2,5-triazo-indene derivatives

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Several 4,6-diphenyl-4,5,6,7-tetrahydro-3-selena-1,2,5-triazo-indene derivatives have been synthesized by the Mannich reaction (condensation) of ethyl methyl ketone, substituted aldehyde and ammonium acetate and selenium dioxide. The chemical structures have been confirmed by means of IR, ^{1}H NMR and mass spectral data. The synthesized compounds have been evaluated for anti-inflammatory, analgesic and antitubercular activity. The compounds have emerged as the most promising active compounds to that of standards. In addition, the inhibition effect increases with the increase in concentration of these compounds.

Keywords: Selenatriazoindene, Anti-inflammatory, Aanalgesic, Antitubercular activities

The chemistry of heterocyclic compound continuous to be an explore field in the organic or pharmaceutical chemistry. The importance of triazole derivatives lies in the field that these have occupied unique position in heterocyclic chemistry, due to its various biological activities. A series of [(4-amino-5-disubstituted-4*H*-1,2,4-triazole-3-yl)thio] alkanoic acid derivatives were synthesized and screened for anti-inflammatory activity[1]. A series of derivatives of [4-amino-3-aryloxyalkyl-5-mercapto-1,2,4-triazole] were synthesized and evaluated for anti-inflammatory activity. A series of 5-[(biphenyl-4-yloxy)methyl]-4-n-substituents-3-mercapto-4*H*-1,2,4-triazole derivatives were synthesized and screened for analgesic activity and that compound showed analgesic activity ranging from 16.9% to 72.8%, whereas the standard drug flurbiprofen showed 69.5% inhibition[2]. Substituted Selena triazo indene are common and they have been used to prepare various heterocyclic ring systems. On the other hand, the interesting pharmacological activities of selenium heterocycles are well known. In addition, selenium is a key component of several major metabolic pathways in human, including thyroid hormone metabolism, antioxidant defense system, and immune function[3]. Also, selenium supplementation could reduce the incidence of various cancer types such as prostate, lung, colon, and liver cancers[4]. It is well known that a number of heterocyclic compounds containing nitrogen and sulfur heteroatoms exhibited a wide variety of biological activities[5]. Moreover, the diazole system is found in numerous antiparasitic, fungicidal, and anti-inflammatory drugs[6]. Among a wide variety of heterocycles triazoles and oxadiazoles have played an important role in medicinal chemistry that have been explored for developing pharmaceutically important molecules. Some of them have received considerable attention as potential antimicrobial agents. Moreover, triazole ring system acquired a special place in the heterocyclic field because it is a frequently encountered structural motif in many pharmacologically relevant heterocyclic compounds. Triazole and oxadiazole have aroused a great deal synthetic effort and with significant biological activity[7].

In the present study, a series of piperidones were synthesized by condensation of ethyl methyl ketone, aromatic aldehyde and ammonium acetate by Mannich reaction. Semi carbazone derivatives of piperidones and 3-methyl-piperidones were synthesized by the reaction of piperidone derivatives with semi carbazide hydrochloride. Then, these were converted into the corresponding selenadiazole compounds. The presence of ketone group in these base compounds was responsible for the development of annelated selenadiazole systems. 2-Substituted benzimidazoles have been synthesized by the condensation of *o*- phenylenediamine hydrochloride with chloroacetic acid and acetic acid. From this, the corresponding hydrazine derivatives were

synthesized. Therefore, series of selenadiazole and their corresponding hydrazine derivatives would result in compounds of potent biological activities.

Experimental Details

All the melting points are uncorrected and were taken in open capillaries on a Gallenkamp apparatus. Majority of the reagents and chemicals procured were of AR quality and were used as received. Infrared spectra were recorded on Bruker IFS 66 V FT-IR. Infrared spectrophotometer was recorded using KBr pellets. ^{1}H NMR spectra were recorded on EM-390 NMR spectrophotometer. Elemental analyses for C, H, N was performed in Heraeus CHN rapid analyzer. The solvents and reagents used for the syntheses were purified by the standard methods. Homogeneity of the compounds were checked by TLC using glass plates coated with silica gel of 0.25 mm thickness. Spots were visualized using iodine chamber and UV light chamber.

Synthesis of compounds

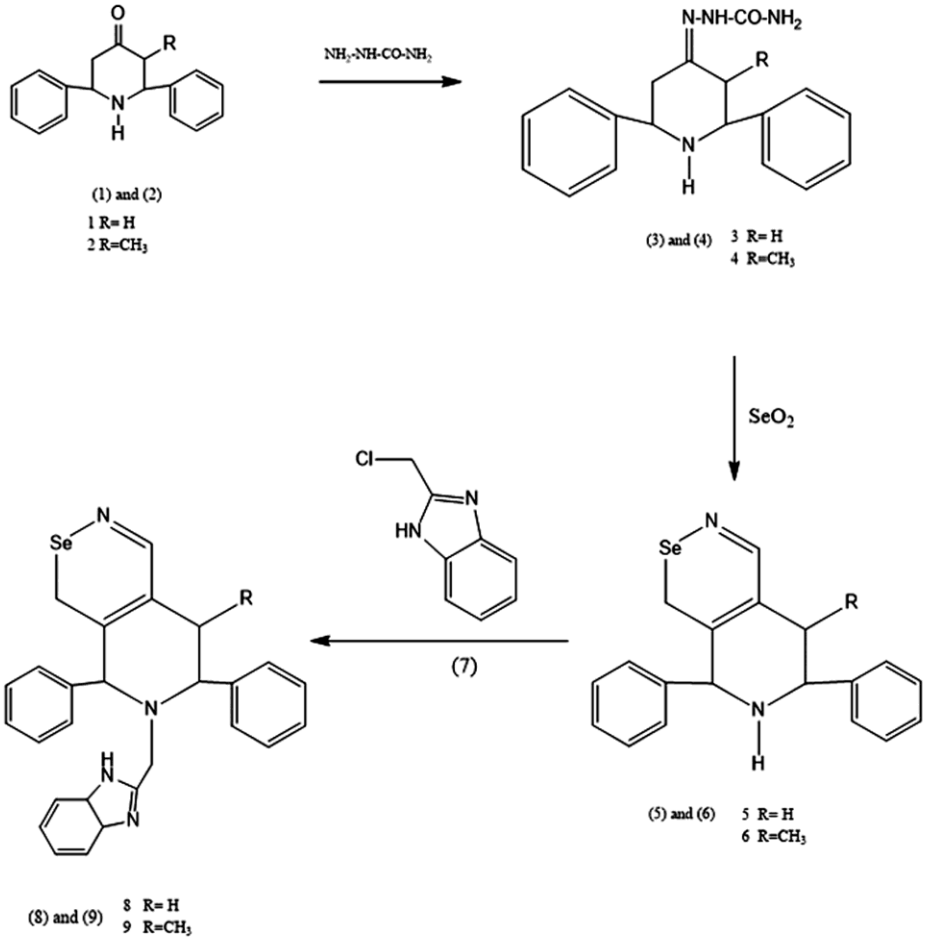
The reaction scheme for the synthesis of compounds **3-9** is shown in Scheme 1.

2-(3-Methyl-2,6-diphenylpiperidin-4-ylidene) hydrazine-1-carboxamide, 3 and 4

A mixture of semi carbazide hydrochloride (1.1 g, 0.01 mol) and piperidin–4-ones (0.01 mol) in ethanol 30 mL) was refluxed for 3 h with continuous stirring. Then the contents were cooled. The product obtained was filtered, washed with water, vacuum dried and recrystallized from absolute ethanol.

8-Methyl-5,7-diphenyl-5,6,7,8-tetrahydro-4*H*-pyrido [4,3] [1,2] selenazine, 5 and 6

To a mixture of semi carbazone derivatives (2 g) in dioxane (5 mL), aqueous solution of selenium dioxide (0.5 g in 0.8 mL) was added with stirring at RT for 3 h. The product obtained was filtered, dried and recrystallized from ethanol. m.p.105-107°C. IR (KBr): 3559, 3162, 3010, 2900, 2348, 1511, 1341, 824, 662, 516 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 9.78



Scheme 1 — Reaction scheme for the synthesis of compounds **3** – **9**

(1H,m,NH), 6.95 – 7.01 (10H,m,ArH), 3.75 – 3.60 (2H,m), 2.65 - 2.58 (1H,m,CH_2), 0.85 (3H,d,CH_3); MS: *m/z* (%) 500.15 (100.0%), 498.15 (52.8%), 501.15 (30.6%), 502.15 (22.4%), 497.15 (21.3%), 496.15 (18.9%), 499.15 (15.4%), 503.15 (5.7%), 500.16 (2.2%), 494.15 (1.8%), 501.14 (1.5%). Elemental Analysis: C, 67.32; H, 5.65; N, 11.22; Se, 15.81%.

2-(Chloromethyl)-1*H*-benzoimidazole, 7

A mixture of *o*-phenylenediamine (10.8 g, 0.1 mole), chloroacetic acid (14.2 g 0.1 mole) and 4N acetic acid (100 mL) was heated under reflux for 45 min. The mixture was allowed to stand overnight. It was diluted with 200 mL of water, cooled and carefully neutralized with 6N ammonium hydroxide solution. The solution was kept cold during the neutralization and stirred well. The product was filtered, water, dried and recrystallized from dioxane.

6-((3a,7a-Dihydro-1*H*-benzo[d]imidazol-2-yl) methyl)-8-methyl-5,7-diphenyl-5,6,7,8-tetrahydro-4*H*-pyrido [4,3] [1,2] selenazine, 8 and 9

A solution of 2,6-diphenyl-4,5,6,7-tetrahydro-3-selena-1,2,5-troazo-indene (0.02 mole) in 100 mL of ether containing 20 mL of absolute ethanol, was added to 2-chloromethyl benzimidazole (1.67g, 0.01 mole) in small portions, keeping the temperature below 15°C. The mixture was heated under reflux for 4 h and then allowed to stand overnight at RT. Dry ether (100 mL) was added, the reaction flask was placed in an ice water bath for 2 h and the precipitate hydrochloride was removed. The filtrate was washed with small amount of water, dried over anhyd. Na_2SO_4 and the solvent evaporated to dryness. The residue was recrystallized from ethanol. m.p.101-103°C. IR (KBr): 3060, 3027, 3024, 2969, 2929, 2869, 2790,1680, 1623, 1557, 1305, 1603,1509, 1453, 1308, 541 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 7.47-6.95 (17H,m,ArH,NH and NH_2), 4.75 (2H,s,N-CH_2), 3.48(1H,d), 3.39(2H,t), 2.80(2H,d,CH_2), 0.8(3H,d, CH_3); MS: *m/z* (%) 368.08 (100.0%), 366.08 (48.0%), 369.08 (22.4%), 364.08 (18.9%), 370.08 (17.7%), 365.08 (15.5%), 367.08 (10.7%), 365.09 (4.1%), 371.08 (4.0%), 366.09 (3.8%), 370.09 (2.3%), 362.09 (1.8%), 368.09 (1.1%); Elemental Analysis: C, 65.39; H, 5.49; N, 7.63; Se, 21.50%.

Pharmacology

Anti-inflammatory studies by the method of Carrageenin induced hind paw oedema in mice

The anti-inflammatory activities of the compounds were studied by the method of Carrageenin induced hind paw oedema in mice. The animals were divided into different groups of six animals each. Mice were treated with different doses of the compounds and 30 min later 0.03 mL of Carrageenin in normal saline was injected into the right hind paw. The animals were sacrificed 4 h after Carrageenin administration. The hind paw was cut at the ankle joint level and weighed. The percentage of inhibition of hind paw oedema was calculated using control and compared with the standard phenylbutazone administered animals. The phenylbutazone was used as a standard for anti-inflammatory studies as much work has been done using it as the standard[8]. The animals received the following doses of the compounds. These compounds were dissolved in 0.2 mL DMSO. At this dose level DMSO was found to have no anti-inflammatory action of its own. The anti-inflammatory effect of the compounds under study is presented in Table 1.

Table 1 — Anti-inflammatory activities of the compounds

Compd	Dose level mg/Kg body weight	Difference in weight of hind paw in mg mean ± SE	Percentage of inhibition
Control	–	36.25 ± 0.6892	–
Phenylbutazone	100	23.08 ± 0.3760	36.33
5	50	24.66 ± 0.1461	31.97
	100	24.00 ± 0..6750	33.80
6	50	26.55 ± 0..6040	26.76
	100	24.67 ± 0.8250	31.97
8	50	24.92 ± 0..2119	25.73
	100	25.43 ± 0.4721	29.85
9	50	28.33 ± 0.4055	21.84
	100	26.21 ± 0..1125	27.70

Each value represents the mean value ± SE of 6 observations

Analgesic studies by tail clip method

Analgesic studies were done by the tail clip method. Albino rats weighing 80-100 g were used. Food and water were withdrawn for 24 h prior to drug administration. All the rats were screened by applying a tail clip (a bull-dog clamp, arms of which were enclosed in a rubber tube) to the base of the tail. Those animals that did not commence continuous efforts to remove the clip within 15 s were rejected. The rats showing positive response were selected and divided into six groups of six rats each. The tail clip was applied to the base of the tail of the animal and observations were made till 120 min after the administration of the test compound. The reaction time is recorded in seconds from the time clip was applied until the animal tries to remove it. Prolongation of the reaction time in the compounds treated animals when compared to the controls gave the analgesic effect. The analgesic effect of the compounds under study is presented in Table 2.

Antitubercular activity

The screening was carried out by using proportion media on LJ media on the H37 Rv strain of *Mycobacterium tuberculosis*. The synthesized derivatives were dissolved in dimethyl sulfoxide to get concentration of 100 µg/mL. Rifampicin and isoniazid were used as standard drugs, which inhibit the growth of *Mycobacterium tuberculosis* at a concentration of 40 µg/mL and 0.2 µg/mL, respectively. The results were read for the first time on the 28th day. The colonies were counted only on the slopes seeded with the inoculum that has produced exact readable counts, results, which are "sensitive" at the 28th day. A second reading was made on the 42nd day to get the definitive result and data are presented in Table 3.

Results and Discussion

The synthesised compounds exhibited moderate to good anti-inflammatory activity. The reaction time for synthesised test compounds with treated animals at a dose level of 50 mg/Kg shows moderate anti-inflammatory activity when compared with the control. However, when the dose level was increased to 100 mg/Kg, the synthesised test compounds show significant anti-inflammatory activity. The analgesic activity of the compound is greatly enhanced by the presence of a substituent in the position 1 of the piperidone ring. The chemical nature of the substituent apparently has a little influence on the activity. The groups such as triazole, selenadiazole produce significant increase (20-30 times) in the

Table 2 — Analgesic activities of the compounds

Compd	Dose level in mg/Kg	Reaction time in minutes observed					
		0	15	30	60	90	120
Control	–	3.08 ±0.204	3.17 ±0.258	3.17 ±0.258	3.33 ±0.258	3.17 ±0.258	3.08 ±0.204
Morphine	15	3.16 ±0.258	6.33 ±0.258	14.40 ±0.490	10.90 ±0.418	9.75 ±0.273	8.16 ±0.258
5	50	2.81 ±0.35	4.66 ±0.34	4.48 ±0.61	6.35 ±0.61	7.61 ±0.34	4.67 ±0.53
	100	3.16 ±0.64	4.92 ±0.73	5.74 ±0.89	6.73 ±0.19	8.12 ±0.34	4.92 ±0.95
6	50	3.09 ±0.63	4.53 ±0.49	6.89 ±0.59	7.58 ±0.25	4.85 ±0.34	3.06 +0.48
	100	3.45 ±0.75	4.71 ±0.16	7.25 ±0.76	7.73 ±0.54	5.26 ±0.95	3.59 ±0.16
8	50	3.76 ±0.51	3.54 ±0.19	3.79 ±0.37	5.75 ±0.41	3.91 ±0.72	3.53 ±0.52
	100	4.25 ±0.72	3.89 ±0.73	4.14 ±0.94	6.13 ±0.06	4.25 ±0.72	4.03 ±0.04
9	50	3.03 ±0.76	4.57 ±0.59	5.38 ±0.68	6.66 ±0.19	4.25 ±0.26	3.96 ±0.15
	100	3.56 ±0.52	4.96 ±0.73	6.04 ±073	5.50 ±0.23	4.58 ±0.06	4.33 ±0.19

Table 3 — Antitubercular activity of the compounds

Compd	Growth (%) observed after 42 days		
	I	II	III
Control	+++	+++	+++
Standard (Rifampicin 40 µg/mL)	–	–	–
Standard (Isoniazid 0.2 µg/mL)	–	–	–
5	+	+	+
6	+	+	+
8	++	++	++
9	+	+	+

Key to symbols: No growth: – (below1%); Mild growth: + (1-50%):
Moderate growth: ++ (505 - 100%); Severe growth: +++ (above 100%)

potency to piperidone. The antitubercular activity tests results for the synthesized compound are reported in Table 3. Compounds **5**, **6** and **9** show activity comparable to that of standard used for assessment of antitubercular activity. Compound **8** has mild activity against *Mycobacterium tuberculosis*.

Conclusion

Several 4,6-diphenyl-4,5,6,7-tetrahydro-3-selena-1,2,5-triazo-indene derivatives (compounds **3**-**9**) have been synthesized by the Mannich reaction and characterized. Compounds **5**, **6** and **9** show activity comparable to that of standard used for assessment of antitubercular activity. Compound **8** has mild activity against *Mycobacterium tuberculosis*.

References

1 Sung K & Lee A R, *J Heterocycl Chem*, 29 (1992) 1101.

2 Kumar H, Javed A S, Khan A S & Amir M, *Eur J Med Chem*, 43 (2008) 2688.

3 Chen T, Wong Y-S, Zheng W & Liu J, *Chem Biol Interact*, 180 (2009) 54. doi: 10.1016/j.cbi.2008.12.010

4 El-Bayoumy K & Sinha R, *Mutat Res*, 551 (2004) 181. doi: 10.1016/j.mrfmmm.2004.02.023

5 Joshi N S, Karale B K & Gill C H, *Chem Heterocycl Compd*, 42 (2006) 681. doi:10.1007/s10593-006-0146-7

6 Baht B A, Dhar K L, Puri S C, Saxena A K I, Shanmugavel M & Qazi G N, *Bioorg Med Chem Lett*, 15 (2005) 3177. doi: 10.1016/j.bmcl.2005.03.121

7 El-Masry A H, Fahmy H H & Ali Abdelwahed S H, *Molecules*, 5 (2000) 1429.

8 Bansal E, Srivastava V K & Kumar A, *Eur J Med Chem*, 36 (2001) 81.