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# Synthesis of tetrahydroindazol-4(5H)one and 7-thione from reaction of functionalized cyclic enaminones with hydrazine

**El Sayed H. El Ashry [1,*], Laila F. Awad [1] and Omayma Kh. Bdeewy [2]**

[1] Chemistry Department, Faculty of Science, Alexandria University Alexandria, Egypt

[2] Chemistry Department, Faculty of Science, Damanhour University, Damanhour, Egypt

**Abstract**: Functionalized enaminones; 3-N-(aryl)amino-1--oxo-cyclohex-2-ene-2-dithiocarboxylates cyclohex-2-en-1-ones and 3-N-(aryl)amino-2-(N-aryl)thioamido-cyclohex-2-en-1-ones were obtained upon reaction of 3-N(aryl)amino-5,5-dimethyl-1-oxo-cyclohex-2-enes with carbon disulfide in presence of sodium hydroxide in DMSO, followed by methylation with dimethyl sulfate or with phenyl and p-bromophenyl isothiocyanates in toluene or under solvent-free condition, respectively. The cyclization of the dithioesters or the thioamides with hydrazine hydrate was accompanied by a displacement of the 3-N- arylamine moiety by a hydrazine group to give 6-hydrazino-4,4-dimethyl-1,3,4,5-tetrahydroindazole-7-thione or 3-N-(aryl)amino-4,5,6,7-tetrahydro-1H-indazole-4(5H)one respectively. Structure of the indazole derivatives formed was further confirmed from their reaction with acetone or p-nitrobenzaldehyde. The new structures were confirmed using $^{1}$HNMR, $^{13}$CNMR, 2DNMR, DEPT experiments and mass spectra.

**Keywords**: Dimedone, Cyclic enaminones, Trans amination, Tetrahydroindazol-4-one, Dithiocarboxylate.

## Introduction

Enaminones have received significant attention in organic synthesis due to their role as valuable precursors for the synthesis of a variety of bioactive heterocyclic compounds [1-8]. The respective dithiocarboxylate derivatives have been extensively utilized in the synthesis of heterocycles and thioglycosides [9-14]. Inazole a pharmacologically important scaffolds serve as structural motifs in drug molecules [15-18]. The diversely of indazole derivatives with a variety of functional groups were found to exhibit a broad spectrum of pharmacological activities [15] such as antimicrobial [19-22], anti-angiogenic, anti-proliferative [23-24] and anti-inflammatory [20,25]. Some indazole derivatives were evaluated for their inhibition activities against fibroblast growth factor receptor FGFR1 [26], a bromodomain-containing protein 4 (BRD4) [27], and as an inhibitor for filamentous temperature sensitive protein Z [21] (FtsZ). A series of tetrahydroindazole were found to have antioxidant activity [28].

Therefore, ongoing interest in the chemistry of enaminones we investigate herein the versatility of some enaminone dithiocarboxylates and enaminone thioamides derived from dimedone as precursors for the synthesis of indazole derivatives.

## Results and Discussion

Enaminones have two electron deficient centers at C-1 and C-3 while C-2 and amino functions are electron rich. They can thus react with both electrophiles and nucleophiles. Therefore, treatment of enaminones **1-6** [29] with carbon disulfide in the presence of sodium hydroxide in dimethyl sulfoxide followed by methylation with dimethyl sulfate afforded the respective methyl 3-N-(aryl)amino-5,5-dimethyl-1-oxo-cyclohex-2-ene-2-dithiocarbo-xylates **7-12**, in 40-73 % yield [11] . The formation of the thioesters **7-12** rather than [3,1-d]benzothiazine-2-thiones **13** was based on their spectral analyses. Thus, the mass spectrum of **11** showed a molecular ion peak at m/z 339.1 ($M^{+\cdot}$) which in agreement with its molecular formula $C_{16}H_{18}NOS_2Cl$. Furthermore, the $^{1}$HNMR spectra of **9, 11** and **12** showed an exchangeable NH proton at the downfield region at δ 13.17–14.60 ppm which excluded structure **13** and agreed with the assigned structure **7-12**.

**Corresponding author*: *El Sayed H. El Ashry*
*Email address: eelashry60@hotmail.com*
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The disappearance of the vinylic C-H proton and the assignment of a characteristic singlet signal of S-Me protons at δ 3.36 ppm of **9** measured in DMSO-$d_6$ and at δ 2.55, 2.57 ppm for **11** and **12**, respectively measured in $CDCl_3$, also confirmed the assigned structure.

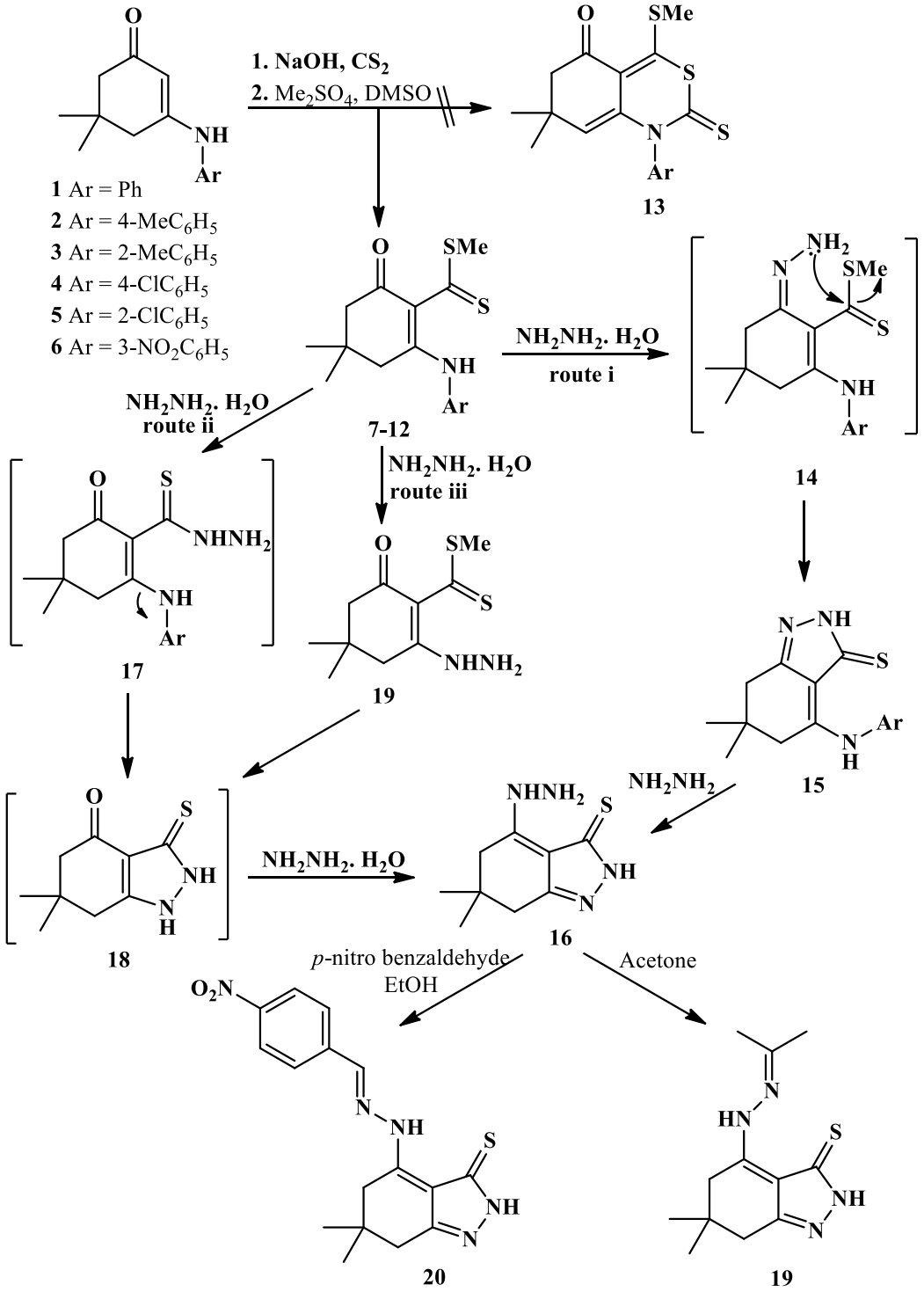
Attempted synthesis of the thiohyrazide derivatives **17** by the reaction of the enamino dithiocarboxylates **7-12** with hydrazine hydrate did not take place, but surprisingly, the products from the different dithiocarboxylates **7-12** have been found to be the same yellow crystalline product. Thus, an indazole ring structure **16** was formed rather than the expected thiohydrazide derivative **17** as deduced from its spectral data. The mass spectrum showed a molecular ion peak at m/z 211.3 ($M^{+\cdot}$+1) which agreed with the molecular formula $C_9H_{14}N_4S$ (210.29). Furthermore, the $^1$H NMR spectrum showed the presence of four exchangeable protons at δ 5.75 ppm ($NH_2$), 12.14 and 12.70 ppm (2 NH) as well as the absence of signals characteristic for aromatic protons. The three singlets at δ 1.00, 2.40 and 2.68 ppm were assigned for two equivalent methyl protons and two methylene protons respectively. The spectral data agreed with the formation of **16** which could be explained to proceed through three different pathways. Hydrazine could react with the carbonyl group of **7-12** to form the hydrazone derivative **14** that upon intramolecular cyclocondensation by nucleophilic displacement of the thiomethyl group will form indazole ring structure **15** that upon further nucleophilic displacement of the arylamino group by hydrazine gave **16 t**hrough an addition-elimination reaction (rout i).

Alternatively, nucleophilic displacement of the thiomethyl group could take place by hydrazine to form the thiohydrazide **17** that spontaneously intermolecularly cyclized with the elimination of arylamine to form **18** whose reaction with hydrazine hydrate gave **16** (rout ii). However, as a consequence of the enaminones, nature [30-32] the hydrazine would attack C-3 first with subsequent elimination of the arylamine moiety to form the intermediate **19** as in route iii. Intramolecular nucleophilic displacement of the thiomethyl group by $NH_2$ of the hydrazine moiety would afford the indazole **18** which reacted with hydrazine to form **16.** Accordingly, route iii represents the most convenient postulated mechanism for this reaction and in agreement with literature data [30-32]. The elimination of arylamine moiety explained the formation of the same product from each of **7-12**. Structure of **16** was further confirmed from X-ray diffraction experiment of the hydrazone derivative **20** derived from **the** reaction of **16** with acetone that showed the structure of the product in full accord with **16**. The acetone derivative **20** is identical with that reported earlier [33].

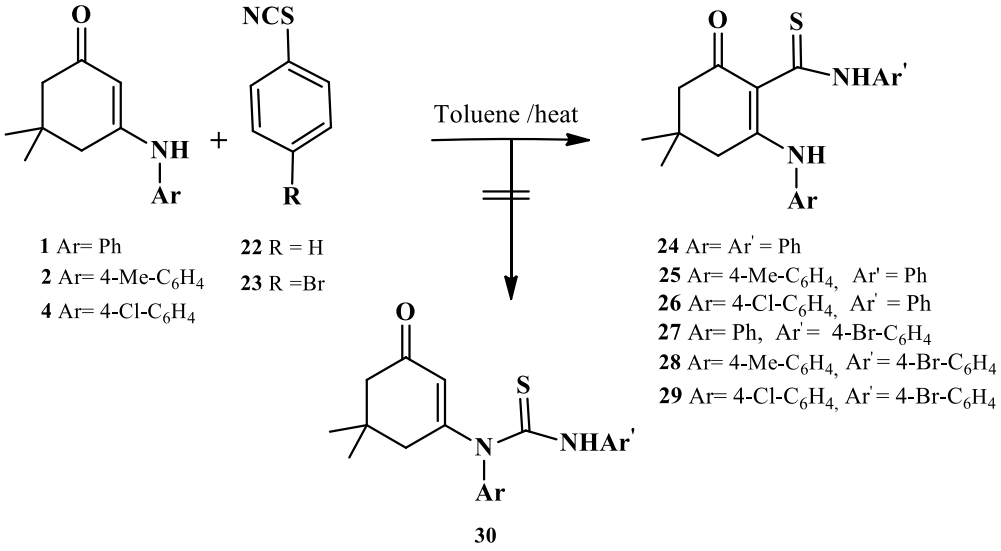
Furthermore, the reaction of **16** with p-nitrobenzaldehyde in boiling ethanol gave a red crystalline hydrazone derivative **21**. The $^1$HNMR spectrum of **21** showed in addition to the signals characteristic for the two methyl groups and the methylene protons of C-3 and C-5, two doublets at δ 8.11 and 8.34 corresponding to the four aromatic protons. At the downfield region, only two exchangeable singlets at δ 12.59 and 14.62 ppm corresponding to two NH protons were assigned. Further support for the structure of compound **21** was verified from its $^{13}$C NMR spectrum where the assignment of signals was supported by $^1$H, $^1$H COSY technique and $^1$H, $^{13}$C shift correlation. Thus, a signal corresponding to the two methyl groups appeared at $\delta_c$ 26.8 ppm which was correlated with their protons that resonated at δ 1.0 ppm whereas the C-4 was resonated at δc 33.1 ppm. Both of the methylene carbons, C-3 and C-5, were assigned based on their correlation with their protons that assigned at δ 2.49 and 3.05 ppm as well as from the DEPT experiment at $\delta_c$ 36.1 and 38.1 ppm. The azomethine carbon resonated at δc 152.6 ppm as confirmed from its correlation with its proton at δ 8.74 ppm. Both of C-6a and C-3a were assigned at δc 106.2 and 162.7 ppm, respectively, whereas, that of C-7 at δc 165.4 ppm.

The attempted reaction of enaminones **1**, **2** and **4** with phenyl isothiocyanate **22** and p-bromophenyl isothiocyanate **23** in toluene under reflux gave the thioamides, **24-29**, respectively in low to moderate yield (33-54%) in addition to the recovery of the respective starting material. An improved yield was obtained when the reaction was carried out under solvent free conditions. Thus, heating of **1, 2** and **4** with **22,** and **1** with **23** without solvent at 160 °C for one hour afforded the respective thioamides **24-27,** respectively in 79-95 % yield as a sole product. The formation of thioamides **24-29** rather than the thiourea derivatives **30** was established from their $^1$HNMR spectra. The disappearance of vinylic H–2 proton and the assignment of two $D_2O$ exchangeable NH protons at δ 14.17-14.74 and 15.81-15.97 ppm for compounds **25-29** whereas that of **24** were assigned at δ 16.71 ppm, confirmed the assigned structure. Both of the C-4 and C-6 protons of dimedone moiety were assigned as either singlet of four protons intensity at δ 2.48 and 2.47 ppm, for compounds **26** and **29**, respectively or as two singlets of two protons intensity each at δ 2.45-2.49 and 2.49-2.50 ppm, for **24**, **25**, **27** and **28** respectively. Signals characteristic for the thiocarbonyl group was

observed in the $^{13}$CNMR spectrum of **25** and **27** at $\delta_c$ 189.85-189.87 ppm whereas C-1 (C=O) was assigned at a higher frequency region at $\delta_c$ 196.26-196.37 ppm. Both of C-2 and C-3 were resonated at $\delta_c$ 104.72-104.74 and 170.84-171.00 ppm, respectively. At the lower frequency region C-4, C-5 and C-6 were assigned at $\delta_c$ 30.25-30.29, 27.82 and 52.31-52.33 ppm, respectively. Furthermore, the mass spectra of **25**, **27** and **29** were in full accord with their assigned structural formula (experimental).




**Scheme 1.** Postulated mechanism for the synthesis of indazole derivatives.



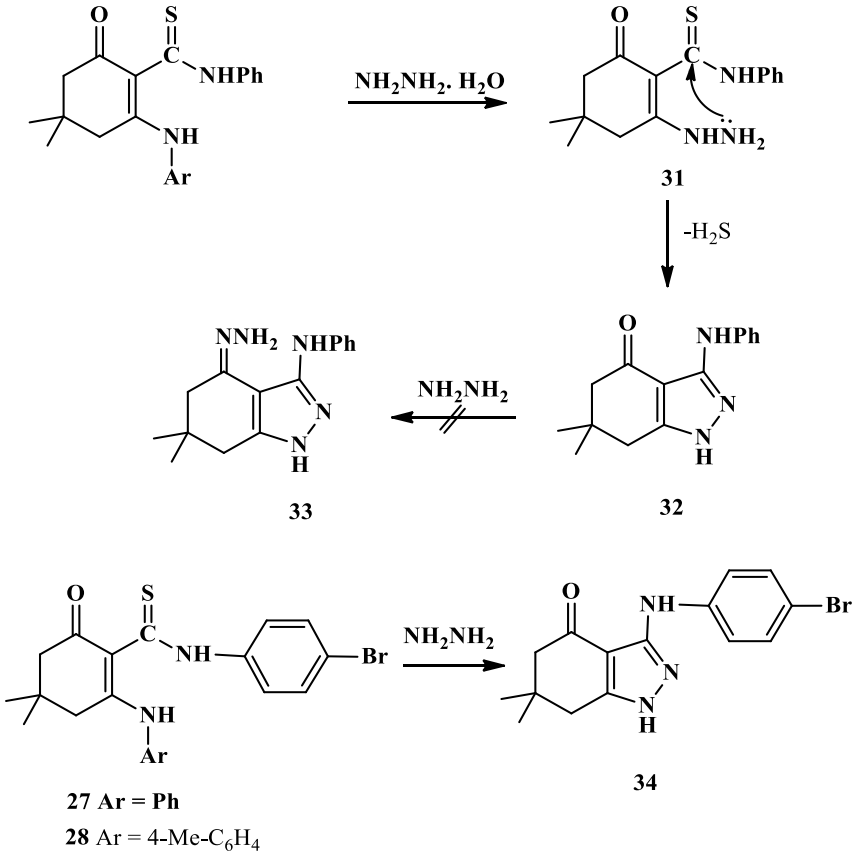

**Scheme 2.** Thioamides from enaminones

Treatment of different substrates **24-26** with hydrazine hydrate in ethanol under reflux for three hours afforded the same product **32**. The formation of a single product can be explained only as a result of the removal of the arylamine moiety at C-3 to give one of two possible structures **32** or **33** respectively. Spectral analyses of the isolated products agreed with structure **32**. The $^{1}$HNMR showed only two $D_2O$ exchangeable NH protons at δ 7.96 ppm as sharp singlet and δ 8.78 ppm as broad one which ruled out structure **33**. Furthermore, the removal of arylamine moiety was confirmed from the absence of 4-methyl group protons of **25** as well as its carbon in the $^{13}$CNMR spectrum as well as the assignment of only five aryl protons at the aromatic area as two triplets and doublet at δ 6.99, 7.36 and 7.53 ppm, respectively. The $^{13}$CNMR spectrum of **32** further supported the displacement of arylamine moiety and cyclization process. Only signals characteristic for one phenyl group carbons were observed at their appropriate position as well as the disappearance of the thione carbonyl carbon.

Moreover, the mass spectrum of **32** obtained from **26** showed a molecular ion peak at m/z 254.31 ($M^{+\cdot}$ -1) which in agreement with the assigned structure **32**. Consequently, the formation of the indazole derivative **32** can be rationalized as a result of an addition-elimination reaction of hydrazine at C-3 with subsequent elimination of the arylamine moiety with the formation of the intermediate **31** that intramolecularly cyclized through an addition-elimination reaction at the thione group C-3 forming the indazole **32** [34]. Although we could not isolate compound **33**, Jirkovshy [34] in a similar reaction using benzylamine instead of arylamine could isolate **33** which upon hydrolysis with HCl gave **32**.

Furthermore compounds **27** and **28** were also subjected to the reaction with hydrazine hydrate to give also a single product **34**. The $^{1}$HNMR showed only four aromatic protons at δ 7.37-7.48 which moreover confirmed the removal of arylamine moiety at C-3. Also, two $D_2O$ exchangeable NH protons were assigned at δ 7.92 and 8.87 ppm. The $^{13}$CNMR spectra of **34** showed signals of C-3 at $\delta_c$ 150.07 ppm whereas C-7a and C-4a were assigned at δ 140.46 and 104.57 ppm, respectively. Other signals are in their appropriate positions.

The formation of **32** rather than the hydrazine derivative **33** was elucidated from the recovery of **32** upon reaction with p-nitrobenzaldehyde. Under these circumstances we could prove that reaction of hydrazine hydrate with thioesters **7-12** or thioamides **24-27** proceed first by attack of hydrazine C-3 with subsequent elimination of arylamine followed by an intramolecular attack of the hydrazine $NH_2$ to the thiocarbonyl group of thioester or thioamide with subsequent elimination of either methylmercaptan or hydrogen sulfide to form indazole ring structure.




**Scheme 3.** 3-N-Arylamino-6,6-dimethyl-3-N-arylamino-6,7-dihydro-1H-indazole-4(5H)-one

## Conclusion

The results considered in this work demonstrate the high synthetic utilities of enaminones as precursors for functionalized derivatives such as dithioesters and thioamides. Selective removal of the arylamino groups from these enaminone derivatives by hydrazine moiety with subsequent cyclization represents a unique method for the synthesis of indazole derivatives.

## Experimental

Melting points were determined with a Mel-Temp apparatus and are uncorrected. TLC was performed on Baker-Flex silica gel 1B-F (1.5-5cm) plates, and the spots were detected by UV light absorption. IR spectra were recorded for all compounds in a matrix of KBr with Perkin-Elmer 1430 spectrometer. $^{1}$H NMR spectra were recorded on Jeol spectrometer (500 MHz), and Bruker AC (300 MHz) spectrometer and the $^{13}$C NMR spectra were recorded on Joel spectrometer (125 MHz) and Bruker AC spectrometer (75 MHz). Chemical shifts (δ) are given in ppm relative to the signal for TMS as an internal standard. Mass spectra were recorded using electron ionization (EI) on a Finnigan MAT 312 spectrometer or Jeol (JMS.600H) instrument. Microanalysis was performed in the unit of microanalysis at Faculty of Science, Cairo University and unit of microanalysis at Faculty of Chemistry, Konstanz University, Germany.

**Methyl 3-N-(aryl)amino-5,5-dimethyl-1-oxo-cyclohex-2-ene-2-dithiocarboxylate (7-12).**

**General Method.**

To a well stirred cold solution of **1-6** (20 mmol) in DMSO (50 mL) and sodium hydroxide solution in water (20 mmol; 2 mL), carbon disulfide (30 mmol) was added in 30 minutes. The mixture was stirred for further 20 minutes below 10 ºC whereby dimethyl sulfate (20 mmol) was added dropwise during 20 min. The reaction mixture was left at room temperature for 1 hour with stirring, diluted with water (200 mL) and acidified with 10 % hydrochloric acid. The resulting precipitate was collected by filtration, dried and recrystallized from methanol to give **7-12**.

**Methyl-5,5-dimethyl-1-oxo-3-N-(phenyl)-aminocyclohex-2-ene-2-dithiocarboxylate (7).** Yellow needles (50 % yield); m. p 154-156 ºC; lit.[11] m. p 161-164 ºC.

**Methyl-5,5–dimethyl-3-N-(4-methylphenyl)-amino-1-oxo-cyclohex-2-ene-2-dithiocarbo-xylate (8).**

Yellow needles (43 % yield); m. p. 180-182 ºC, lit.[11] m. p. 185-187 ºC.

**Methyl-5,5-dimethyl-3-N-(2-methylphenyl)-amino-1-oxo-cyclohex-2-ene-2-dithiocarbo-xylate (9).**

Orange needles (58 % yield); m. p. 188-190 ºC. IR (KBr) 3400 (NH); 1652 $cm^{-1}$ (CO); $^1$H NMR (DMSO-$d_6$, 500 MHz): $\delta_H$ ppm = 0.95 (s, 6 H, 2 Me), 1.9 (s, 2 H, $CH_2$), 2.03 (s, 2 H, $CH_2$), 2.5 (s, 3 H, Me), 3.36 (s, 3 H, SMe), 6.5 (d, 1H, J 7.65 Hz, Ar-H), 6.99 (t, 1H, J 7.65 Hz, Ar-H), 7.14-7.29 (m, 2 H, Ar-H), 14.6 (s, 1H, $D_2O$ exchangeable HN).

Analysis calcd. for $C_{17}H_{21}N$ O $S_2$ (319.478): C, 63.91; H, 6.62; N, 4.38; S 20.07. Found: C, 63.88; H, 6.51; N, 4.29; S, 20.08.

**Methyl-5,5-dimethyl-3-N-(4-chlorophenyl)-amino-1-oxo-cyclohex-2-ene-2-dithiocarbo-xylate (10).**

Yellow needles (40 % yield); m. p. 158-160 ºC, lit.[11] m. p. 160-162 ºC.

**Methyl 5, 5-dimethyl-3-N-(2-chlorophenyl)-amino-1-oxo-cyclohex-2-ene-2-dithiocarbo-xylate (11).**

Orange needles (73% yield); m. p. 162-164 ºC. IR (KBr) 3400 (NH); $^1$H NMR ($CDCl_3$, 500 MHz): $\delta_H$ ppm = 1.01 (s, 6 H, 2 Me), 2.36 (s, 2 H, $CH_2$), 2.43 (s, 2 H, $CH_2$), 2.55 (s, 3 H, SMe), 7.23 (dd, 1 H, J 9.2 Hz, Ar-H), 7.34-7.35 (m, 2 H, Ar-H), 7.52 (dd, 1 H, J 9.95 Hz, Ar-H), 13.17 (s, 1H, $D_2$o exchangeable, NH). MS (EI), m/z (%): 339.1 (30, $M^{+\cdot}$), 292 (100, $M^{+\cdot}$- SMe**).**

Anaysisl calcd. for $C_{16}H_{18}Cl$ N O $S_2$ (339.895): C, 56.54; H, 5. 34; N, 4.12; S, 18.87. Found: C, 56.30; H, 5. 58; N, 4.31; S, 18.75.

**Methyl 5,5-dimethyl -3-N(3-nitrophenyl)-amino-1-oxo-cyclohex-2-ene-2-dithiocarbo-xylate (12).**

Yellow needles (60 % yields); m. p. 176-178 ºC. $^1$H NMR ($CDCl_3$, 500 MHz): $\delta_H$ ppm = 1.04 (s, 6 H, 2 Me), 2.46 (s, 2 H, $CH_2$), 2.52 (s, 2 H, $CH_2$), 2.57 (s, 3 H, SMe), 7.53, (dd, 1 H, J 6.9 Hz, Ar-H), (t, 1H, J 8.4 Hz, Ar-H), 8.06 (t, 1 H, J 2.3 Hz, Ar-H), 8.22 (dd,1 H, J 6.9 Hz, J 1.5 Hz, Ar-H), 13.56 (s, 1 H, $D_2O$ exchangeable, NH).

Analysis calcd. for $C_{16}H_{18}$ $N_2$ $O_3$ $S_2$ (350.45): C, 54.83; H, 5.17; N, 7.99; S, 18.29. Found: C, 54.71; H, 4.97; N, 7.88; S, 18.01.

**6-Hydrazino-4,4-dimethyl-1,3,4,5-tetrahydro-indazol-7-thione (16).**

A solution of **7-12 (**0.9 mmol) in ethanol (15 mL) was treated with hydrazine hydrate (2 mL). The mixture was heated under reflux for 1 hr., then left to cool. The product was filtered and crystalized from methanol to give **16** in 40 % yield from **7,** 58 % yield from **8,** 40% yield from **9,** 73% yield from **10**, 48% from **11** and 60% from **12**, m. p. 177-179 ºC; IR (KBr) 3160 (NH); 1664 $cm^{-1}$ (C=N); $^1$H NMR (DMSO-$d_6$, 300 MHz): $\delta_H$ ppm =1.0 (s, 6 H, 2 Me), 2.40 (s, 2 H, $CH_2$), 2.68 (s, 2 H, $CH_2$), 5.75 (s, 2 H, $D_2O$ exchangeable $NH_2$), 12.14, 12.70 (2 s, 2 H, $D_2O$ exchangeable, 2 NH).

Ms (EI) m/z (%) 211.3 (14, $M^{+\cdot}$+1), 179 (22, $M^{+\cdot}$-$NH_2NH_2$).

Analysis calcd. for $C_9H_{14}N_4S$ (210.269): C, 51.39; H, 6.71; N, 26.64. Found: C, 51.72; H, 6.41; N, 26.63.

**6,6-Dimethyl-4-(2-(propan-2-ylidene)-hydrazinyl)-6,7-dihydro-2H-indazole-3(5H)-thione (20).**

A solution of 6-hydrazino-4, 4-dimethyl-1,3,4,5-tetrahydroindazol-7-thione (**16**) (0.20 g) in methanol (20 mL) was treated with acetone (5 mL) and then heated under reflux for 1 h. The product was recrystallized from a mixture of acetone and methanol to give yellow crystals, m. p. 262 ºC, identical with that reported earlier, lit.[34] m. p. 262 ºC.

**4,4-Dimethyl-6-(4-nitrophenyl)hydrazono-1,3,4,5-tetrahydroindazol-7-thione (21).**

A solution of **16** (0.6 mmol) and p-nitrobenzaldehyde (0.68 mmol) in methanol (15 mL) was heated under reflux for 20 minutes. A red crystals were separated, filtered while hot, washed with methanol and recrystallized from methanol/ dimethylformamide to give **21** (50% yield); m. p. 236-238 ºC;

IR (KBr) 3404, 3112 (NH) and 1618 $cm^{-1}$ (C=N), $^1$H NMR (DMSO-$d_6$, 300 MHz): $\delta_H$ ppm = 1.0 (s, 6 H, 2 Me), 2.49 (s, 2 H, $CH_2$), 3.05 (s, 2 H, $CH_2$), 8.11 (d, 2 H, J= 8.6 Hz, Ar-H), 8.34 (d, 2 H, J= 8.6 Hz, Ar-H), 8.74 (s,1H, CH=N), 12.59, 14.62 (2s, 2H, $D_2O$ exchangeable, 2 NH);

$^{13}$C NMR $\delta_c$ ppm: 26.8 (2 Me), 33.1 (C-4), 36.1, 38.1 (C-3, C-5), 106.2 (C-6a), 122.9 (C-2, C-5, Ar-C), 137.5 (C-4, Ar-C) 147.5 (C-1`, Ar-C), 150.4 (C-6), 152.6 (HC=N), 162.7 (C-3a), 165.4 (C-7).

Anaysis calcd. for $C_{16}H_{17}N_5SO_2$ (343.406): C, 55.95; H, 4.99; N, 20.39. Found: C, 55.77; H, 4.78; N, 20.25.

**3-N-(Aryl)amino-2-(N-aryl)thioamido-5,5-dimethylcyclohex-2-en-1-one (24-29).**

**General method a.** A mixture of enamines **1, 2** and **4** (10 mmol), and aryl isothiocyanate **22** and **23** (10 mmol) in toluene (20 mL) was refluxed for 20 hr. The reaction mixture was left to cool, and the unreacted enamines were separated by filtration. The filtrate was concentrated under reduced pressure. The syrup obtained was triturated with methanol to give **24-29** that were recrystallized from ethanol.

**General method b.** A mixture of enamines **1, 2** and **4** (10 mmol) and aryl isothiocyanate **22** and

**23** (10 mmol) was heated under reflux for 1 hr in an oil bath at 160 °C. The glassy product obtained was then crystallized from ethanol to give **24-27**.

**5,5-Dimethyl-3-N-(phenyl)amino-2-(N-phenyl)thioamido-cyclohex-2-en-1-one (24).**
It was obtained as pale yellow crystals in 47% yield from method a and in 92% yield from method b; mp 160-162 ºC lit.[35] m. p. 168-169 ºC; $^1$H NMR ($CDCl_3$, 500 MHz): $\delta_H$ ppm = 1.04 (s, 6 H, Me), 2.49 (s, 4 H, 2 $CH_2$), 7.17 (d, 2 H, Ar-H), 7.24-7.27 (m, 2 H, Ar-H), 7.34-7.48 (m, 5 H, Ar-H), 16.7 (2 s, 2 H, $D_2O$ exchangeable NH).
Analysis calcd. for $C_{21}H_{22}N_2OS$ (350.476): C, 71.96; H, 6.33; N, 7.99; S, 9.15. Found: C, 71.80; H, 6.20; N, 7.65; S, 8.85.

**5,5-Dimethyl-2-(N-phenyl)thioamido-3-(4-methylphenyl)amino-cyclohex-2-en-1-one (25).**
It was obtained as colorless crystals in 33% yield from method a and in 79% yield from method b; m. p. 162-164 ºC;
$^1$H NMR ($CDCl_3$, 500 MHz) $\delta_H$ppm = 1.03 (s, 6 H, 2Me), 2.39 (s, 3 H, Me), 2.46 (s, 2 H, $CH_2$), 2.49 (s, 2 H, $CH_2$), 7.07 (d, 2 H, J= 8.6 Hz, Ar-H), 7.22-7.26 (m, 3 H, Ar-H), 7.39 (t, 2 H, J= 7.65, Ar-H), 7.46 (d, 2 H, J= 7.3 Hz, Ar-H), 14.17, 15.91 (2 s, 2 H, $D_2O$ exchangeable 2 NH).
$^{13}$CNMR($CDCl_3$) $\delta_c$ ppm: 21.11(4-Me), 27.82 (2Me), 30.25 (C-5), 42.93 (C-4), 52.31 (C-6), 104.72 (C-2), 119.63, 125.89, 127.79, 130.26, 131.80, 134.14, 137.87, 138.27 (Ar-C0, 171.00 (C-3), 189.85 (C=S),196.26 (C-1).
MS, m/z (%): 364.2 (33,$M^{+\cdot}$), 331.2 (78, $M^{+\cdot}$-SH), 241.2 (100, 331.2$^{+\cdot}$ - PhN).
Analysis calcd. for $C_{22}H_{24}N_2OS$ (364.496): C, 72.49; H, 6.64; N, 7.69; S, 8.84. Found: C 71.99; H 6.56; N 7.83; S 8.69.

**3-(4-Chlorophenyl)amino-5,5-dimethyl-2-(N-phenyl)thioamido-cyclohex-2-en-1-one (26).**
It was obtained as pall yellow crystals in 33% yield from method a and in 96% yield from method b ; m. p. 166-168 ºC;
$^1$H NMR ($CDCl_3$, 500 MHz: $\delta_H$ ppm = 1.04 (s, 6 H, 2 Me), 2.48 (s, 4 H, 2 $CH_2$), 7.13 (d, 2 H, J= 8.6 H, Ar-H), 7.24-7.27 (m, 2 H, Ar-H), 7.38-7.42 (m, 3 H, Ar-H), 7.46 (d, 2 H, J= 7.65, Ar-H), 14.61, 15.97 (2s, 2H, $D_2O$ exchangeable NH).
Analysis calcd. for $C_{21}H_{21}ClN_2OS$ (348.923): C, 65.52; H, 5.50; N, 7.28; S, 8.33. Found: C, 65.44; H, 5.56; N, 7.48; S, 8.54.

**2-(N-4-Bromophenyl)thioamido-5,5-dimethyl-3-N-(phenyl)amino-cyclohex-2-en-1-one (27).**
It was obtained as colorless crystals in 33% yield from method a and in 95 % yield from method b; m. p. 202-204 ºC;
$^1$H NMR ($CDCl_3$, 500 MHz): $\delta_H$ ppm = 1.03 (S 6 H, 2 Me), 2.46 (2, 2 H, $CH_2$), 2.50 (s, 2 H, $CH_2$), 7.19 (d, 2 H, J= 7.65 Hz, Ar-H), 7.38 (d, 3 H, J= 8.7 Hz, Ar-H), 7.45 (t, 2 H, J= 7.65 Hz, Ar-H) 7.51 (d, 2 H, J= 8.6 Hz, Ar-H), 14.74, 15.93 (2s, 2H, $D_2O$ exchangeable 2 NH).
$^{13}$CNMR($CDCl_3$) $\delta_c$ ppm: 27.81 (2Me), 30.29 (C-5), 43.03 (C-4), 52.33 (C-6)104.74 (C-2), 119.73, 126.15, 127.78, 127.82, 129.69, 131.82, 136.83, 138.22 (Ar-C), 170.84 (C-3), 189.87 (C=S) 196.37 (C=O).
MS: m/z (%) 430.3 (10, $M^{+\cdot}$ +1), 397.3 ($M^{+\cdot}$ –$H_2S$ ),241 (25, 397.3- $C_6H_4Br$).
Analysis calcd. for $C_{21}H_{21}Br\ N_2OS$ (429.382): C, 58.74; H, 4.93; N, 6.52; S, 7.47. Found: C, 58.64; H, 4.57; N, 6.19; S, 7.18.

**2-N-(4-Bromophenyl)thioamido-6,6-dimethyl-3-N-(4-methylphenyl)amino-cyclohex-2-en-1-one (28).**
It was obtained as pale yellow crystals in 37% yield from method a; m.p. 208-210 °C
$^1$H NMR ($CDCl_3$, 500 MHz): $\delta_H$ ppm = 1.03 (s, 6 H, 2 Me), 2.39 (s, 3 H, Me), 2.46 (s, 2 H, $CH_2$), 2.49 (s, 2 H, $CH_2$), 7.06 (d, 2 H, J= 8.65 H, Ar-H), 7.25 (m, 3 H, Ar-H), 7.38 (d, 2 H, J= 8.6 Hz), 7.50 (d, 2H, J= 8.6 Hz), 14.73, 15.81 (2s, 2H, $D_2O$ exchangable, 2NH).
MS, m/z (%): 442.6 (15.2, $M^{+\cdot}$ ), 409.1 (20.4, $M^{+\cdot}$- $H_2S$ ), 272.2 (45, $M^{+\cdot}$-Br-$C_6H_4$-N).
Analysis calcd. For $C_{22}H_{23}N_2$ (443.402): C, 59.59; H, 5.23; N, 6.32; S, 7.23. Found: C, 59.09; H, 5.27; N, 5.98; S, 6.94.

**2-N-(4-Bromophenyl)thioamido-3-N-(4-chlorophenyl)amino-5,5-dimethyl-cyclohex-2-en-1-one (29).**
It was obtained as pall yellow crystal in 54% yield from method a; m. p. 185-187 °C ;
$^1$H NMR ($CDCl_3$, 500 MHz): $\delta_H$ppm = 1.04 (s 6 H, 2 Me), 2.47 (s, 4 H, 2 $CH_2$), 7.13 (d, 2 H, J= 8.65 Hz, Ar-H), 7.37 (d, 2 H, J= 8.6 Hz, Ar-H), 7.43 (d, 2H, J 8.65, Ar-H), 7.51 (d, 2 H, J= 8.6 Hz, Ar-H), 7.67 (d, 1 H, J= 8.6 Hz, Ar-H), 14.67, 15.91 (2 s, 2H,$D_2O$ exchangeable, N-H).
Analysis calcd. For $C_{21}H_{20}BrCl\ N_2OS$ (463.829): C, 54.37; H, 4.35; N, 6.04; S, 6.91. Found: C, 54.64; H, 4.01; N, 5.87; S, 6.95.

**3-N-(Aryl)amino-6,6-dimethyl-6,7-dihydro-1H-indazole-4(5H)ones (32) and (34).**
A mixture of compounds **24-28** (0.2 mmol) and hydrazine hydrate in ethanol (10 mL) was heated under reflux for 3h. The resulting solution was then concentrated under reduced pressure. The solid obtained was filtered off and crystallized for ethanol.

**6,6-Dimethyl-3-N-(phenyl)amino-6,7-dihydro-1H-indazole-4(5H)one (32):**

It was obtained as colorless crystals in 69, 46 and 45% yield from **24**, **25** and **26**, respectively, m. p. 272-273 °C; lit [35] m.p. 270-271°C,
IR 3464 (NH); 1618 $cm^{-1}$ (C=O),
$^1$HNMR ($CDCl_3$, 500 MHz): δH ppm = 1.17 (s, 6H, 2Me), 2.40 (s, 2H, $CH_2$), 2.68 (s, 2H, $CH_2$), 6.99 (t, 1H, Ar-H), 7.33-7.36 (m, 2H, Ar-H), 7.53 (d, 2H, Ar-H), 7.96 (s, 1H, $D_2O$ exchangeable, NH),
$^{13}$CNMR ($CDCl_3$) δc ppm: 28.54 (2Me), 35.42 (C-6), 36.14 (C-7), 51.70 (C-5), 104.80 (C-4a), 117.38, 121.32, 129.19, 140.55 (Ar-C), 155.2 (C-3), 193.52 (C-4), MS, m/z (%): 254.1 (40, $M^{+\cdot}$ -1), 162 ($M^{+\cdot}$ - $PhNH_2$).
Analysis calcd for $C_{15}$ $H_{17}$ $N_3O$ (255.31): C, 70.56; H, 6.71; N, 16.46. Found: C, 70.44; H, 6.50; N, 16.30.

**3-N-(4-Bromophenyl)amino-6,6-dimethyl-6,7-dihydro-1H-indazole-4(5H)one (34).**
It was obtained as colorless crystals in 71% yield from **27** and 50% yield from **28**; m.p. 256-258 °C; $^1$HNMR ($CDCl_3$, 300 MHz): δH ppm = 1.10 (s, 6H, 2Me), 2.37 (s, 2H, $CH_2$), 2.67 (s, 2H, $CH_2$), 7.42-7.48 (m, 4H, Ar-H), 7.92 (s, 1H, $D_2O$ exchangeable, NH), 8.87(bs, 1H, $D_2O$ exchangeable, NH); $^{13}$CNMR (DMSO-$d_6$) δc ppm: 28.46 (2Me), 34.56 (C-6), 36.21 (C-7), 51.92 (C-5), 104.57 (C-4a), 111.51, 119.19, 131.50, 132.02, 132.26, 141.29 (Ar-C), 150.02 (C-7a), 150.07 (C-3), 192.99 (C-4).
Anaysis calcd. for $C_{15}H_{16}Br$ $N_3O$ (334.216 ) C, 53.91; H, 4.83; N, 12.57. Found: C, 53.74; H, 4.51; N, 12.30.

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