A Novel Synthetic Protocol for the Heteroannulation of Oxocarbazole and Oxoazacarbazole Derivatives through Corresponding Oxoketene Dithioacetals

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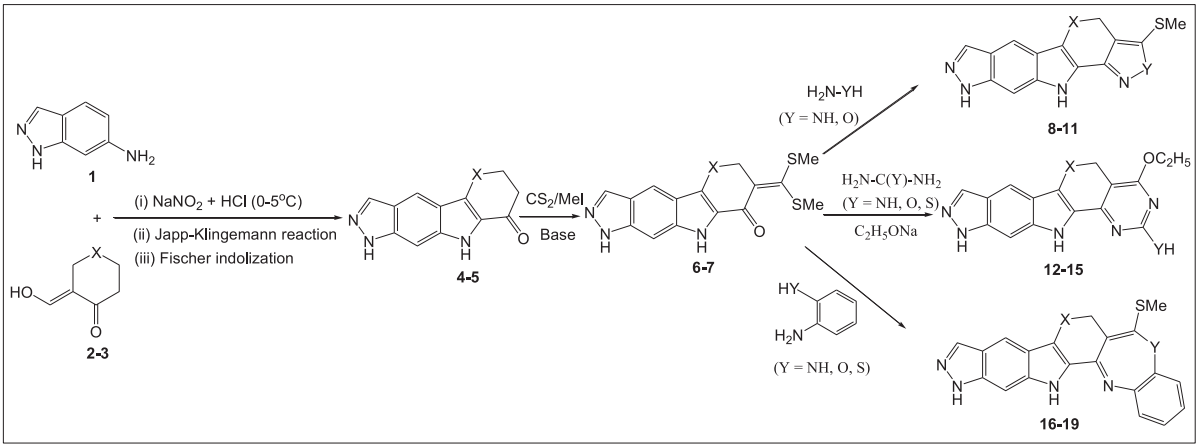


An efficient novel strategy for the heteroannulation of 6,7-dihydropyrazolo[3,4-b]carbazol-8(*1H,5H,9H*)-one **4** and 5-*N*-benzyl-6,7-dihydropyrazolo[3,4-b]carbazol-8(*1H,9H*)-one **5** has been developed to allow the incorporation of pyrazole, isoxazole, pyrimidine, benzodiazepine, and benzothiazepine rings through their corresponding oxoketene dithioacetal derivatives **6** and **7**, respectively.

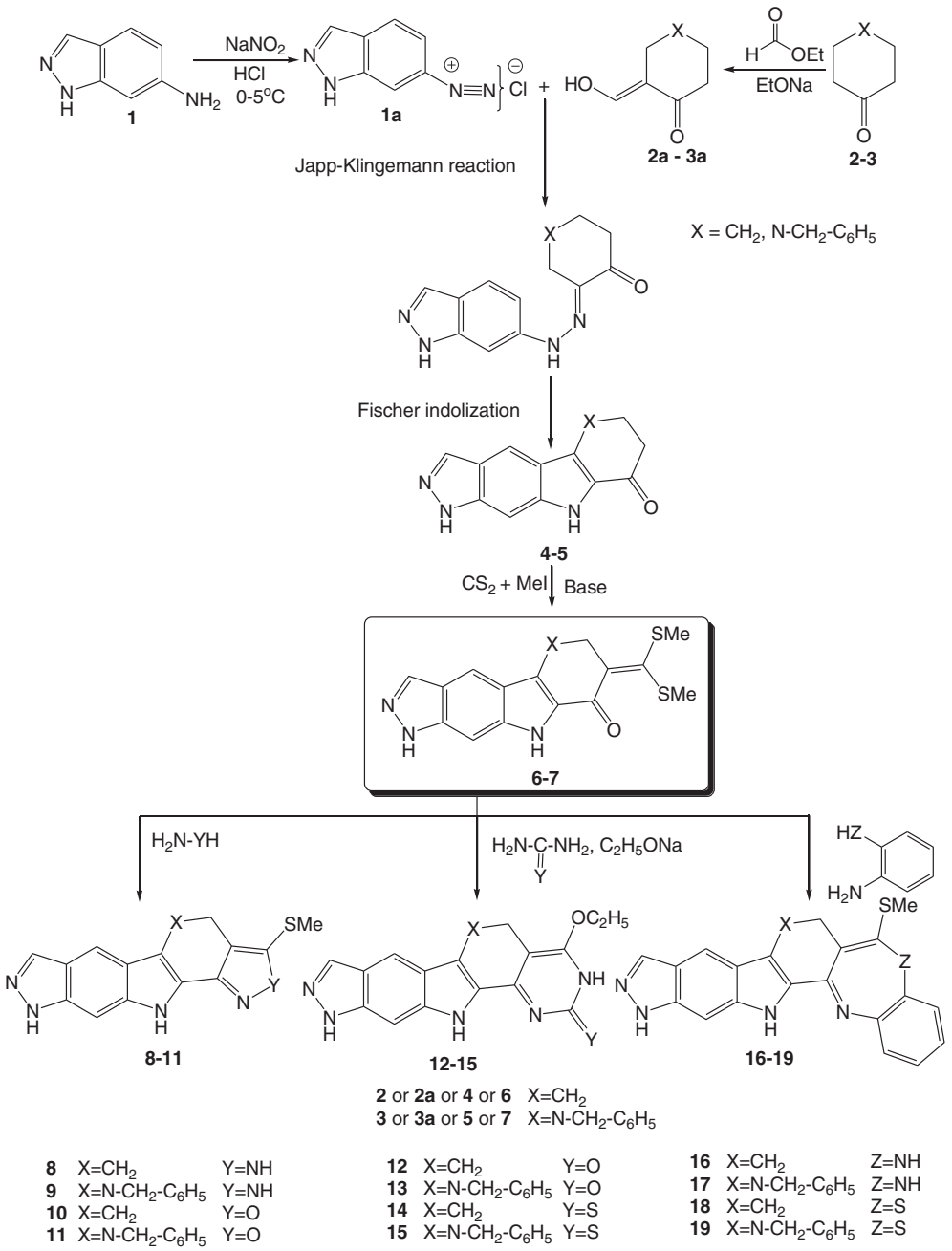
INTRODUCTION

Development of compound libraries of medicinally potent agents from "privileged heterocyclic scaffolds" is a rapidly emerging subject in medicinal chemistry [1]. Benzodiazepines have been recognized to belong to this class [2]. Recently, bio-efficacy of pyrimidines and their derivatives has been widely explored on account of their applications as privileged structures, a term introduced by Evans *et al*. [3a], that are capable of providing ligands to a number of functionally and structurally discrete biological receptors [3b,c]. Ubiquity of carbazoles, azacarbazoles, and pyridocarbazoles (such as ellipticine, olivacine, carbaquinacine, *etc*.) in the chemical literature [4] is undoubtedly a consequence of multifarious biological response, which they elicit in combating a variety of body ailments. Recent demonstrations that some of their derivatives can be used as anti-HIV [5] agents have stimulated further interest in this nucleus from yet another perspective. This has stimulated enormous research efforts to be directed toward the synthesis of their structural analogs where different constitution and biological activity in new materials could allow them to be used as novel chemotherapeutic agents [6]. Condensed heterocyclic systems containing indoles [7], carbazoles [8], azacarbazoles [9], pyrazoles [10], isoxazoles [11], pyrimidines [12], diazepines [13], oxazepines [14], thiazepines [15], and so forth have attracted the attention of chemists on account of significant medicinal properties associated with these nuclei. In view of the prodigious range of activities of these molecules, it was considered of interest to develop libraries of compounds from carbazoles and azacarbazoles that contained the fused pyrazole nucleus on one side and the bioactive pharmacophores such as the isoxazole, pyrazole, pyrimidine, benzodiazepines, benzothiazepines, and so forth on the other side. The presence of the aforementioned moieties on the both sides in the same molecular framework could contribute significantly in enhancing the biopotency by providing an additive effect to the overall efficacy in the resulting molecules.

As a part of an ongoing endeavor to create novel heterocyclic scaffolds through simple and straightforward expedient routes, we have explored the application of oxoketene dithioacetals-based cyclization reactions to the heteroannulation of oxocarbazole and oxoazacarbazole nucleus. Herein, we describe in this article, the preliminary results from studies of our synthetic efforts that have allowed an efficient synthetic entry to the novel heterocyclic materials depicted in Scheme 1.

The oxocarbazole **4** and oxoazacarbazole **5** derivatives required for this study, were readily obtained from commercially available 5-nitroindazole. The conventional reduction

Scheme 1. Synthesis of heteroring fused pyrazolo-carbazoles and azacarbazoles from oxoketene dithioacetals.



of 5-nitroindazole gave its amine analog (i.e., 5-amniindazole **1**) which furnished corresponding diazonium chloride (**1a**) after diazotization. Application of the Japp–Klingemann reaction on aryldiazonium salts with 2-hydroxymethylene cyclohexanone has been demonstrated in the literature [16] to provide an easy access to the corresponding aryl hydrazones, whose subsequent cyclocondensation in acid under the conditions of Fischer indolization offers a very convenient synthetic entry to the corresponding oxocarbazole derivatives [17]. The use of 3-hydroxymethylene-4-piperidone in this synthesis affords the corresponding oxoazacarbazoles [16]. A protocol based on this technique of oxocarbazole and oxoazacarbazole ring formation when applied to 5-indazolyldiazonium chloride **1a** with 2-hydroxymethylene cyclohexanone **2a** and further to 1-*N*-benzyl-3-hydroxymethylene-4-piperidone **3a** generated pyrazolo-annulated oxocarbazole **4** and oxoazacarbazole **5**, respectively (Scheme 1).

RESULTS AND DISCUSSION

The synthetic plan conceived for the preparation of the materials **8–19** (Scheme 1) required it to be executed in three stages. The first stage of this strategy involved the conversion of 5-indazolyldiazonium chloride **1a** to the pyrazolo-fused oxocarbazoles **4** and oxoazacarbazoles **5**, respectively. These were realized by the interaction of indazolyldiazonium chloride **1a** with 2-hydroxymethylene cyclohexanone **2a** and 1-*N*-benzyl-3-hydroxymethylene-4-piperidone **3a**, respectively, under the conditions of Japp–Klingemann reaction followed by the Fischer indolization [7] of the resulting hydrazones with Kent's acid (HCl : AcOH; 1 : 4 v/v). The compounds **4** and **5** were intern-obtained following the reported procedure that consisted of treating cyclohexanone **2** and 1-*N*-benzyl-4-piperidone **3**, respectively, with ethyl formate in presence of sodium ethoxide. The second stage of the strategy required the conversion of **4** and **5** to the corresponding oxoketene dithioacetals derivatives **6** and **7** from their reaction with CS_2 and CH_3I in presence of a base. Oxoketene dithioacetals are useful 3-carbon 1,3-dipolarophiles that have been extensively employed in the literature for the preparation of five-membered, six-membered, and seven-membered heterocyclic rings from its reaction with bidentate nucleophiles such as hydrazine hydrate, hydroxylamine hydrochloride, urea, thiourea, *o*-phenylenediamine, *o*-aminophenol, and *o*-aminothiophenol [18]. Application of this strategy on oxoketene dithioacetal derivatives **6** and **7** with the indicated bidentate nucleophiles gave the pyrazoles (**8** and **9**), isoxazoles (**10** and **11**), pyrimidines (**12–15**), and azepines (**16–19**), respectively, in high yield and purity (Scheme 1). The structure of compounds **6**, **7** and **8–19** was established on the basis of their microanalysis results as well as their IR, ^{1}H NMR and MS spectral data. The spectral data of these compounds unequivocally established the structures of these molecules. The IR spectra of **4** and **5** showed the presence of the strong absorption band near 1700 cm^{-1} for CO group. The formation of corresponding oxoketene dithioacetals **6** and **7** was confirmed by the appearance of the band near about 680 cm^{-1} for C–S stretching. As pyrazole, isoxazole, pyrimidine, diazepine, and thiazepine rings in **8–19** resulted from the condensation involving the carbonyl group of **6** and **7** with bidentate nucleophiles, the disappearance of the CO absorption band in IR spectra in compounds **8–19** provided strong evidence in favor of the formation of these compounds. The most diagnostic evidence for the formation of compounds **8–19** was provided by the appearance of a signal in the region of δ 10.1 for the indole NH in the ^{1}H NMR spectra in all compounds (NH proton of indazole nucleus appeared at a much downfield region δ 12.0 ppm). The appearance of the M^+ peak corresponding to their molecular weight in MS spectra confirmed the formation of the compounds and established their structures.

CONCLUSION

In conclusion, two noteworthy features from the strategy employed in synthesis of the reported compounds are apparent from our study. Firstly, it established that the Fischer indolization of 1-(5-indazolyl)-2-(1′-oxo-2′-cyclohexyl) hydrazone and 1-(5-indazolyl)-2-(1′-*N*-benzyl-4′-oxo-3′-piperidinyl) hydrazone provided a very convenient synthetic entry to the corresponding difficultly accessible pyrazolo-fused oxocarbazole and oxoazacarbazole derivatives **4** and **5**, respectively. It established further the versatility of the Japp–Klingemann reaction to provide a one-pot synthetic protocol to the preparation of heteroaryl hydrazones (on to the adjacent methylene carbon of a cyclic carbonyl species), which are not accessible by the conventional procedures. Secondly, it provided an easy access to the formation of corresponding oxoketene dithioacetals derivatives and their reaction with bidentate nucleophiles to give pyrazole, isoxazole, pyrimidine, and azepine condensed carbazole and azacarbazole derivatives of biological interest in high purity and yield.

EXPERIMENTAL

Melting points were determined on an open capillary and are uncorrected. The IR spectra were recorded on Schimadzu FTIR-8400S (Prague, Czech Republic). ^{1}H NMR spectra were recorded in DMSO-d_6 and in $CDCl_3$ on Bruker DRX-300 spectrometer (Billerica, MA) using TMS as internal reference and values are expressed in δ ppm. Mass spectra were taken on a Jeol SX-102 mass spectrometer (Tokyo, Japan) at 70 eV. 5-aminoindazole required in synthesis was prepared from the reduction [19] of commercially available 5-nitroindazole.

General procedure for the preparation of oxocarbazoles and oxoazacarbazoles (4–5).

Part I. Preparation of 1-(5-indazolyl)-2-(1′-N-benzyl-4′-oxo-3′-piperidinyl)hydrazone using Japp–Klingemann reaction. A solution of 5-indazolyl amine 1 (1.08 g, 1.0 mmol) in aqueous HCl (2 mL conc. HCl in 4 mL water) was treated with a cold saturated solution of sodium nitrite (0.7 g in 2 mL water) while the temperature was kept at 0–5°C. The solution was kept aside for 10 min. It was then added portion wise to an ice-cooled mixture containing (E)-1-*N*-benzyl-3-hydroxymethylene-4-piperidone **3a** (2.17 g, 1.0 mmol), sodium acetate trihydrate (1.80 g), methanol (10 mL) and water (6 mL) over a period of 0.5 h with stirring. The contents were allowed to stand for further 0.5 h and the resulting solid mass was filtered, washed with water, dried, and recrystallized from ethanol. 1-(5-indazolyl)-2-(1′-oxo-2′-cyclohexyl) hydrazone was prepared from 2-hydroxymethylidene cyclohexanone **2a** by adopting the same methodology.

Part II. General procedure for the cyclization of hydrazones by Fischer indolization. A solution of crude hydrazone (0.68 g, 0.01 mmol) suspended in a mixture of acetic acid and HCl (4 : 1) was refluxed on a pre-heated oil bath at 125–130°C for 0.5–1 h. The contents were then cooled and poured into ice-cold water with stirring and basified with ammonia till

neutralization. The separated brown solid was purified by passing through a column of silica gel using 50% benzene in pet ether as eluant.

6,7-Dihydropyrazolo[2,3-b]carbazol-8(1H,5H,9H)-one (4). The compound **4** (1.46 g, 65%) was obtained following the procedure described in parts I and II. mp 238–40°C. IR (KBr) : ν 3290, 2920, 1720, 1510, 1020 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$ and DMSO-d_6): δ 12.4 (1H, s, NH of pyrazole ring), 10.1 (1H, s, NH of indole ring), 8.20 (1H, s, CH of pyrazole ring), 7.85 (2H, s, ArH), 2.43 (2H, t, $J = 6.5$ Hz, CH_2), 2.10 (2H, m, CH_2), 1.89 (2H, t, $J = 6.5$ Hz, CH_2); MS: *m/z* 225 [M^+]; anal. calcd./found for $C_{13}H_{11}N_3O$: C, 69.32/69.22; H, 4.92/4.78; N, 18.52/18.46.

5-N-Benzyl-6,7-dihydropyrazolo[2,3-b]-5-azacarbazol-8 (1H,9H)-one (5). The compound **5** (2.21 g, 70%) was also obtained as compound **4**. mp 277–79°C. IR (KBr): ν 3220, 2910, 1735, 1520, 1040 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$ and DMSO-d_6): δ 11.9 (1H, s, NH of pyrazole ring), 10.8 (1H, s, NH of indole ring), 8.15 (1H, s, CH of pyrazole ring), 7.79 (2H, s, ArH), 7.72–7.66 (5H, m, ArH), 4.32 (2H, s, CH_2 of benzyl hydrogen), 3.39 (2H, t, $J = 6.4$ Hz, CH_2), 2.63 (2H, t, $J = 6.4$ Hz, CH_2) ppm; MS: *m/z* 316 [M^+]; anal. calcd./found for $C_{19}H_{16}N_4O$: C, 72.13/72.02; H, 5.10/4.03; N, 17.71/17.62.

Preparation of 7-(bis(methylthio)methylene)-6,7-dihydropyrazolo [4,3-b]carbazol-8(1H,5H,9H)-one (6). A mixture of 6,7-dihydropyrazolo[2,3-b]carbazol-8(*1H,5H,9H*)-one 4 (2.04 g, 6.0 mmol) and CS_2 (1.14 mL, 6.0 mmol) was added to a well stirred and cold suspension of t-BuOK (1.34 g, 1.0 mmol) in dry benzene (4.0 mL) and DMF (3.0 mL), and the reaction mixture was allowed to stand at room temperature for 4 h. Methyl iodide (2.0 mL, 1.0 mmol) was gradually added with stirring and external cooling (exothermic reaction), and the reaction mixture was allowed to stand for 4 h at room temperature with occasional shaking and then refluxed on a water bath for 3 h. The aqueous portion was extracted with benzene, combined the extracts and washed with water, dried over anhydrous sodium sulfate and the solvent was removed by distillation. The compound **6** (1.545 g, 58%) obtained was recrystallized from ethanol. mp 310–12°C. IR (KBr): ν 3230, 2925, 1680, 1540, 1050, 680 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$ and DMSO-d_6): δ 11.7 (1H, s, NH of pyrazole ring), 10.06 (1H, s, NH of indole ring), 8.10 (1H, s, CH of pyrazole ring), 7.80 (2H, s, ArH), 2.46 (2H, t, $J = 6.5$ Hz, CH_2), 2.30 (2H, t, $J = 6.5$ Hz, CH_2), 2.13 (6H, s, CH_3) ppm; MS: *m/z* 329 (15%) [M^+]; anal. calcd./found for $C_{16}H_{15}N_3OS_2$: C, 58.33/58.24; H, 4.59/4.51; N, 12.87/12.79, S, 10.60/10.53.

Preparation of 7-(bis(methylthio)methylene)-5-N-benzyl-6,7-dihydropyrazolo[2,3-b]-5-azacarbazol-8(1H,9H)-one (7). The compound **7** (1.936 g, 60%) was prepared by using stratgey followed for preparation of compound **6**. mp 288–90°C. IR (KBr): ν 3370, 2960, 1800, 1500, 1025, 690 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$ and DMSO-d_6): δ 12.01 (1H, s, NH of pyrazole ring), 9.9 (1H, s, NH of indole ring), 8.20 (1H, s, CH of pyrazole ring), 7.81 (2H, s, ArH), 7.78–7.74 (5H, m, ArH), 3.68 (2H, s, CH_2), 2.26 (2H, s, CH_2), 2.14 (6H, s, CH_3) ppm; MS: *m/z* 420 (15%) [M^+]; anal. calcd./found for $C_{22}H_{20}N_4OS_2$: C, 62.83/62.75; H, 4.79/4.71; N, 13.43/13.34, S, 15.45/15.35.

Preparation of 3-methylthio-2,4,5,9,11-pentahydropyrazolo[3,4-a]pyrazolo[3,4-b]carbazole (8). Hydrazine hydrate (5.0 mL, 2.0 mmol) and compound **6** (1.77 g, 2.0 mmol) were taken in 25–30 mL of ethanol and refluxed for 3 h. The solvent was removed and the residue was dissolved in 10 mL of chloroform and dried over anhydrous sodium sulfate and filtered. On removal of solvent, the compound **8** (1.65 g, 71%) was obtained. mp 204–206°C. IR (KBr): ν 3340, 2920, 1605, 1020, 680 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$ and DMSO-d_6): δ 13.1 (1H, s, NH of pyrazole ring), 12.2 (1H, s, NH of pyrazole ring), 10.08 (1H, s, NH of indole ring), 8.44 (1H, s, CH of pyrazole ring), 7.78 (2H, s, ArH), 2.86 (2H, t, $J = 6.5$ Hz, CH_2), 2.79 (2H, t, $J = 6.5$ Hz, CH_2), 2.13 (3H, s, CH_3) ppm; MS: *m/z* 295 (17%) [M^+]; anal. calcd./found for $C_{15}H_{13}N_5S$: C, 61.01/60.91; H, 4.44/4.32; N, 23.41/23.33, S, 10.86/10.74.

Preparation of 5-N-benzyl-3-methylthio-2,4,9,11-tetrahydropyrazolo[3,4-a]pyrazolo[3,4-b]-5-azacarbazole (9). Compound **9** (1.57 g, 76%) was prepared from compound **7** using same method adopted for preparation of the compound **8**. mp 172–74°C. IR (KBr): ν 3300, 2990, 1530, 1040, 690 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$ and DMSO-d_6): δ 13.3 (1H, s, NH), 12.2 (1H, s, NH), 10.3 (1H, s, NH), 8.16 (1H, s, CH), 7.76 (2H, s, ArH), 7.72–7.65 (5H, m, ArH), 4.29 (2H, s, CH_2), 4.14 (2H, s, CH_2), 2.34 (3H, s, CH_3) ppm; MS: *m/z* 386 (16%) [M^+]; anal. calcd./found for $C_{21}H_{18}N_6S$: C, 68.55/68.46; H, 4.97/4.81; N, 21.75/21.64; S, 8.30/8.21.

Preparation of 3-methylthio-2,4,5,9,11-pentahydroisoxazolo [3,4-a]pyrazolo[3,4-b]carbazole (10). Hydroxylamine hydrochloride (2.78 g, 4.0 mmol) was added to sodium methoxide (3.24 g, 6.0 mmol) in absolute methanol (30 mL) and stirred for 10 min. The compound **6** (1.77 g, 4.0 mmol) was added and the mixture was refluxed for 5 h. Most of the methanol was evaporated under reduced pressure and the mixture was poured into ice-cold water. The solid separated was filtered, washed with diethyl ether, and dried. Recrystallization from ethanol gave 10 (1.18 g, 72%). mp 169–70°C. IR (KBr): ν 3450, 2995, 1600, 1532, 900, 700 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$ and DMSO-d_6): δ 12.2 (1H, s, NH), 10.2 (1H, s, NH), 8.4 (1H, s, CH), 7.79 (2H, s, ArH), 2.76 (2H, t, $J = 6.5$ Hz, CH_2), 2.59 (2H, t, $J = 6.5$ Hz, CH_2), 2.33 (3H, s, CH_3) ppm; MS: *m/z* 296 (12%) [M^+]; anal. calcd./found for $C_{21}H_{18}N_6S$: C, 60.79/60.68; H, 4.08/3.99; N, 18.91/18.83; S, 10.82/10.74.

Preparation of 5-N-benzyl-3-methylthio-2,4,9,11-tetrahydroisoxazolo[3,4-a]pyrazolo[3,4-b]-5-azacarbazole (11). The compound **11** (1.47 g, 70%) was prepared by using compound **7** instead of **6**. IR (KBr): ν 3420, 3000, 1600, 1520, 890, 680 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$ and DMSO-d_6): δ 11.9 (1H, s, NH), 10.2 (1H, s, NH), 8.36 (1H, s, CH of pyrazole ring), 7.82 (2H, s, ArH), 7.76–7.72 (5H, m, ArH), 4.39 (2H, s, CH_2), 4.19 (2H, s, CH_2), 2.24 (3H, s, CH_3) ppm; MS: *m/z* 387 (12%) [M^+]; anal. calcd./found for $C_{21}H_{17}N_5OS$: C, 68.37/68.26; H, 4.69/4.60; N, 18.08/17.98; S, 8.28/8.21.

Preparation of 4-ethoxy-2-hydroxy-5,6,10,12-tetrahydropyrimido [4,5-a]pyazolo[3,4-b]carbazole (12). To a mixture of urea (0.12 g, 2.0 mmol), sodium ethoxide (0.14 g, 2.0 mmol), and ethanol (25–30 mL) was added compound **6** (0.68 g, 2.0 mmol) and the reaction mixture was refluxed for 10–14 h. The solvent was removed by distillation and residue was treated with glacial acetic acid (4–5 mL just enough to dissolve the sodium salt of the pyrimidine) and refluxed for 15 min. The reaction mixture was poured on crushed ice and precipitate obtained was purified by crystallization with chloroform to give 12 (0.65 g, 76%). mp 185–86°C. IR (KBr): ν 3610, 3330, 2990, 1530, 1550, 1040 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$ and DMSO-d_6): δ 12.1 (1H, s, NH), 10.02 (1H, s, NH), 8.28 (1H, s, CH), 7.78 (2H, s, ArH), 4.02 (1H, s, OH), 3.73 (2H, q, $J = 7.5$ Hz, CH_2), 2.52 (2H, t, $J = 6.5$ Hz, CH_2), 2.32 (2H, t, $J = 6.5$ Hz, CH_2), 1.25

(3H, t, $J = 7.5$ Hz, CH_3) ppm; MS: *m/z* 321 (18%) [M^+]; anal. calcd./found for $C_{17}H_{15}N_5O_2$: C, 63.54/63.41; H, 4.71/4.63; N, 21.66/21.56.

Preparation of 6-N-benzyl-4-ethoxy-2-hydroxy-5,10,12 trihydropyrimido[4,5-a]pyazolo[3,4-b]-6-azacarbazole (13). The compound **13** (1.45 g, 61%) was prepared using **7** and adopting same method that was used for the preparation of **12**. mp 167–70°C. IR (KBr) : ν 3390, 1605, 1547, 1045, 1700, 1155 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$ and DMSO-d_6): δ 11.8 (1H, s, NH), 10.2 (1H, s, NH), 7.97 (1H, s, CH), 7.68 (2H, s, ArH), 7.06–7.14 (5H, m, ArH), 4.97 (1H, s, OH), 4.24 (2H, s, CH_2), 3.62 (2H, s, CH_2), 3.24 (2H, q, $J = 7.5$ Hz, CH_2), 1.22 (3H, t, $J = 7.5$ Hz, CH_3) ppm; MS: *m/z* 412 (16%) [M^+]; anal. calcd./found for $C_{23}H_{20}N_6O_2$: C, 66.98/66.87; H, 4.89/4.79; N, 20.38/20.31.

Preparation of 4-ethoxy-2-mercapto-5,6,10,12-tetrahydropyrimido [4,5-a]pyazolo[3,4-b]carbazole (14). In place of urea, thiourea (0.152 g, 2.0 mmol) was taken with the compound **6** to give the compound **14** (0.687 g, 76%). mp 210–12°C. IR (KBr): ν 3400, 1600, 1550, 1050, 1150 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$ and DMSO-d_6): δ 12.2 (1H, s, NH), 10.06 (1H, s, NH), 8.44 (1H, s, CH), 7.79 (2H, s, ArH), 3.89 (2H, q, $J = 7.5$ Hz, CH_2), 3.00 (1H, s, SH), 2.83 (2H, t, $J = 6.5$ Hz, CH_2), 2.22 (2H, t, $J = 6.5$ Hz, CH_2), 1.68 (3H, t, $J = 7.5$ Hz, CH_3) ppm; MS: *m/z* 337 (12%) [M^+]; anal. calcd./found for $C_{17}H_{15}N_5SO$: C, 60.52/60.44; H, 4.48/4.36; N, 20.63/20.53; S, 9.45/9.41.

Preparation of 6-N-benzyl-4-ethoxy-2-mercapto-5,8,12-trihydropyrimido[4,5-a]pyrazolo[3,4-b]-6-azacarbazole (15). Compound **15** (1.41 g, 64%) was prepared from **7** by using same methodology that was used for preparation of **14**. IR (KBr): ν 3390, 1605, 1547, 1045, 1455, 1155 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$ and DMSO-d_6) δ: 12.1 (1H, s, NH), 9.98 (1H, s, NH), 8.12 (1H, s, CH), 7.70 (2H, s, ArH), 7.09–7.16 (5H, m, ArH), 4.18 (2H, s, CH_2), 3.91 (1H, s, SH), 3.64 (2H, s, CH_2), 3.29 (2H, q, $J = 7.5$ Hz, CH_2), 1.25 (3H, t, $J = 7.5$ Hz, CH_3) ppm; MS: *m/z* 428 (25%) [M^+]; anal. calcd./found for $C_{23}H_{20}N_6OS$: C, 64.47/64.38; H, 4.70/4.65; N, 19.61/19.55; S, 7.48/7.41.

Preparation of 7-methylthio-1,5,6,8,14-pentahydropyrazolo [3,4-b]carbazolo[7,8-b]diazepine (16). A mixture of *o*-phenylenediamine (1.08 g, 1.0 mmol), compound **6** (0.68 g, 2.0 mmol) and ethanol (20–25 mL) was refluxed for 4–5 h. The solvent was distilled under reduced pressure and the residue was quenched in crushed ice. It was extracted with chloroform, washed with water, and dried over anhydrous sodium sulfate to give 16 (0.6 g, 66%). mp 173–74°C. IR (KBr): ν 3380, 2950, 1580, 1470, 1050, 680 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$ and DMSO-d_6): δ 12.2 (1H, s, NH), 10.6 (1H, s, NH), 8.30 (1H, s, CH), 7.76 (2H, s, ArH), 7.62-7.58 (4H, m, ArH), 4.14 (1H, s, NH), 2.37 (2H, t, $J = 6.5$ Hz, CH_2), 2.19 (2H, t, $J = 6.5$ Hz, CH_2), 1.66 (3H, s, CH_3) ppm, MS: *m/z* 371 (30%) [M^+]; anal. calcd./found for $C_{21}H_{17}N_5S$: C, 67.90/67.81; H, 4.61/4.54; N, 18.75/18.68, S, 8.63/6.56.

Preparation of 5-N-benzyl-7-methylthio-1,6,8,14-tetrahydropyrazolo [3,4-b]5-azacarbazolo[7,8-b]diazepine (17). The compound **17** (0.65 g, 72%) was prepared from the *o*-phenylenediamine and compound **7** using the aforementioned procedure. mp 176–77°C. IR (KBr): 3300, 2990, 1530, 1405, 1040, 695 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$ and DMSO-d_6): δ 12.1 (1H, s, NH), 10.1 (1H, s, NH), 8.16 (1H, s, CH), 7.84 (2H, s, ArH), 7.78–7.72 (4H, m, ArH), 7.69–7.61 (5H, m, ArH), 4.00 (1H, s, NH), 4.25 (2H, s, CH_2), 3.73 (2H, s, CH_2), 1.98 (3H, s, CH_3) ppm; MS: *m/z* 462 (21%) [M^+]; anal. calcd./found for $C_{21}H_{22}N_6S$: C, 70.11/70.01; H, 4.79/4.72; N, 18.09/17.98; S, 6.93/6.87.

Preparation of 7-methylthio-1,5,6,8,14-pentahydropyrazolo [3,4-b]carbazolo[7,8-b]thiazepine (18). Instead of *o*-phenylenediamine, *o*-aminothiophenol (1.25 g, 1.0 mmol) reacted with the compound **6** to give **18** (0.72 g, 74%). mp 185–87°C. IR (KBr): ν 3370, 3030, 1620, 1500, 1325, 1150, 650 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$ and DMSO-d_6): δ 12.3 (1H, s, NH), 10.3 (1H, s, NH), 8.36 (1H, s, CH), 7.81 (2H, s, ArH), 7.72–7.69 (4H, m, ArH), 2.25 (2H, t, $J = 6.5$ Hz, CH_2), 2.43 (2H, t, $J = 6.5$ Hz, CH_2), 1.88 (3H, s, CH_3) ppm; MS: *m/z* 388 (27%) [M^+]; anal. calcd./found for $C_{21}H_{16}N_4S_2$: C, 64.92/64.82; H, 4.15/4.08; N, 14.16/14.04; S, 16.41/16.35.

Preparation of 5-N-benzyl-7-methylthio-1,6,8,14-tetrahydropyrazolo[3,4-b]5-azacarbazolo[7,8-b]thiazepine (19). Similarly the compound **19** (0.96 g, 68%) was prepared from *o*-aminothiophenol and the compound **7**. mp 83–84°C. IR (KBr): ν 3380, 3010, 1560, 1680, 1210 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$ and DMSO-d_6): δ 12.08 (1H, s, NH), 10.2 (1H, s, NH), 8.16 (1H, s, CH), 7.82 (2H, s, ArH), 7.78–7.72 (4H, m, ArH), 7.69–7.65 (5H, m, ArH), 4.25 (2H, s, CH_2), 3.77 (2H, s, CH_2), 2.15 (3H, s, CH_3) ppm; MS: *m/z* 479 (19%) [M^+]; anal. calcd./found for $C_{27}H_{21}N_5S_2$: C, 67.61/67.54; H, 4.41/4.36; N, 14.51/14.44, S, 13.32/13.25.

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