

Synthesis of Novel 1-Substituted and 1,9-Disubstituted-1,2,3,4-tetrahydro-9H-Carbazole Derivatives as Potential Anticancer Agents

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Abstract: Condensation of 1-acetyl-1,2,3,4-tetrahydro-9H-carbazole (**2**) with some amino compounds furnished the corresponding imino derivatives **3a-e**. Compound **3a** reacted with chloroacetic acid and underwent cyclization to give the thiazolidine derivative **5**. Also, treatment of **3c** with thionyl chloride caused cyclization to yield the [1,2,6]thiadiazino derivative **6**, which gave the corresponding N-formyl derivative **7** upon heating with ethyl formate. In addition, interaction of **3d** with ethyl cyanoacetate yielded the monoamide of malonic acid derivative **8**. Acylation of carbazole **1** with succinoyl chloride or phenylacetyl chloride produced the corresponding azepine (**11**) and 1,9-diphenyl acetyl derivatives (**14**), respectively. Compounds **11**, **14** were further reacted to give the carbazole derivatives **12**, **13** and **15a,b**. The cytotoxic activity for some of the prepared compounds against breast cancer B₂₀ is discussed.

Keywords: Carbazole derivatives, thiadiazino derivatives, cytotoxic activity

Introduction

The clinical need for therapeutic agents which restore or enhance an immune response in immunocompromised patients such as that which occurs in viral infections, cancer, autoimmune diseases and acquired immune deficiency syndrome (AIDS) has led to the search for novel immunostimulants [1]. Interferon- γ (IFN- γ) is a potent activator of the immune system and has been used in the treatment of infections in human. A fused pyrrolo[2,3-c]carbazol-6-one (Figure 1) reportedly potentiates the INF- γ induction of MHC-class π molecules [2].

Other carbazole derivatives like ellipticin, and the alkaloids vincristine and vinblastine have a well established role in the treatment of cancer [3-8]. The present work is a part of our program aimed at developing new approaches for synthesis of fused heterocyclic systems containing the carbazole moiety and evaluating their anticancer activity.

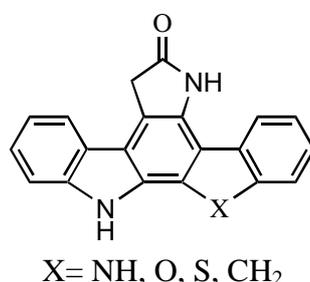


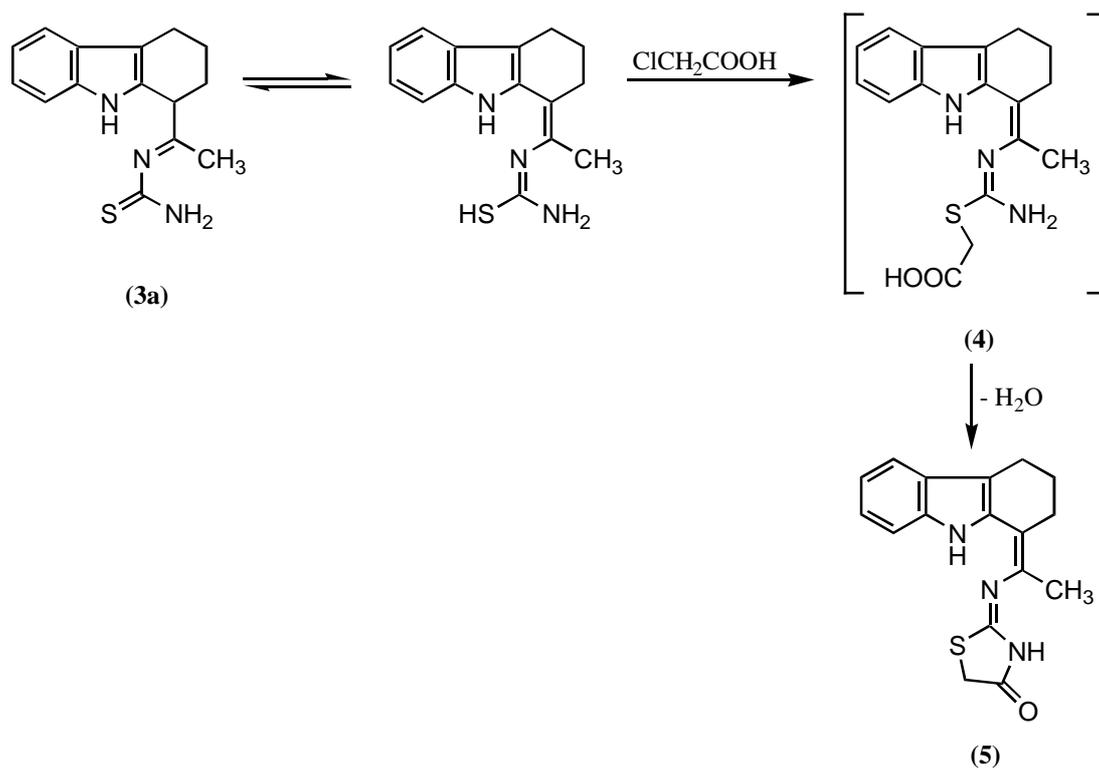
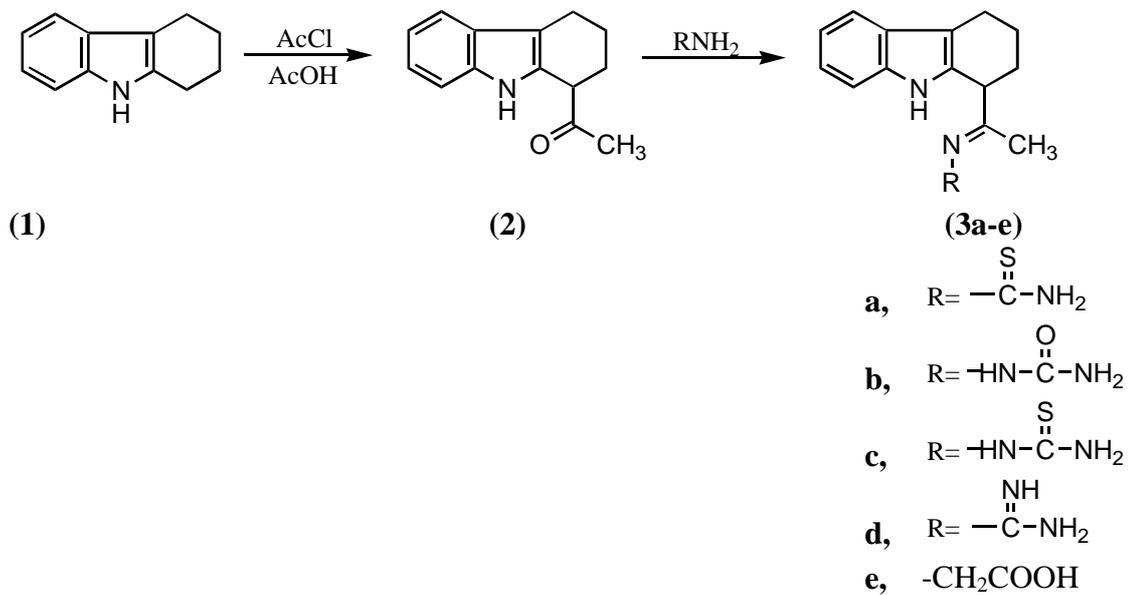
Figure 1

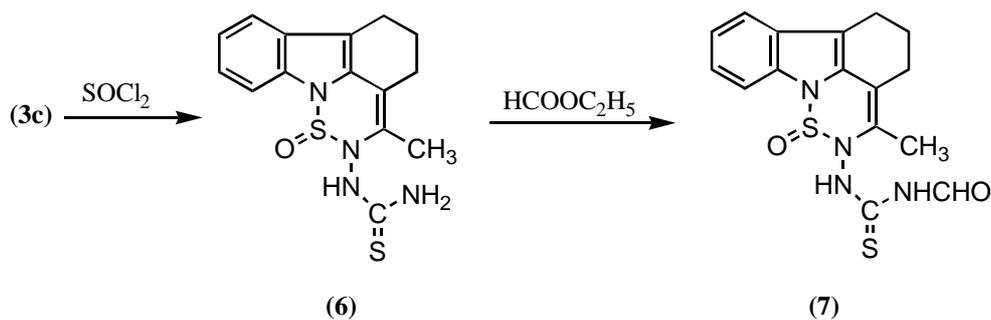
Results and Discussion

Acetylation of 1,2,3,4-tetrahydrocarbazole (**1**) using acetyl chloride and glacial acetic acid afforded 1-acetyl tetrahydrocarbazole (**2**). Compound **2** was used as a starting material in the synthesis of many heterocyclic compounds containing a carbazole moiety. Thus, condensation of **2** with thiourea, thiosemicarbazide, guanidine hydrochloride and glycine produced the corresponding imino derivatives **3a-e**.

Interaction of **3a** with chloroacetic acid can proceed via the formation of an intermediate mercaptoacetic acid derivative **4** which cyclizes through elimination of water to give the thiazolidine derivative **5**, as depicted in Scheme 1. Its mass spectrum showed the expected m/z 296 ($M-15$ (CH_3); 0.5%).

Treatment of **3c** with thionyl chloride in pyridine caused cyclization to furnish [1,2,6]thiadiazin-5-oxide derivative **6** [9] via elimination of two moles of HCl. The elemental analysis and spectral data are in good agreement with the proposed structure. Formylation of **6** was done by treatment with ethyl formate to yield the N-formyl derivative **7** (Scheme 1). The mass spectrum of compound **7** exhibited a molecular ion peak at m/z 360 (M^+ , 1.0%), 344 ($M-16$ (O), 0.7%).





Scheme 1

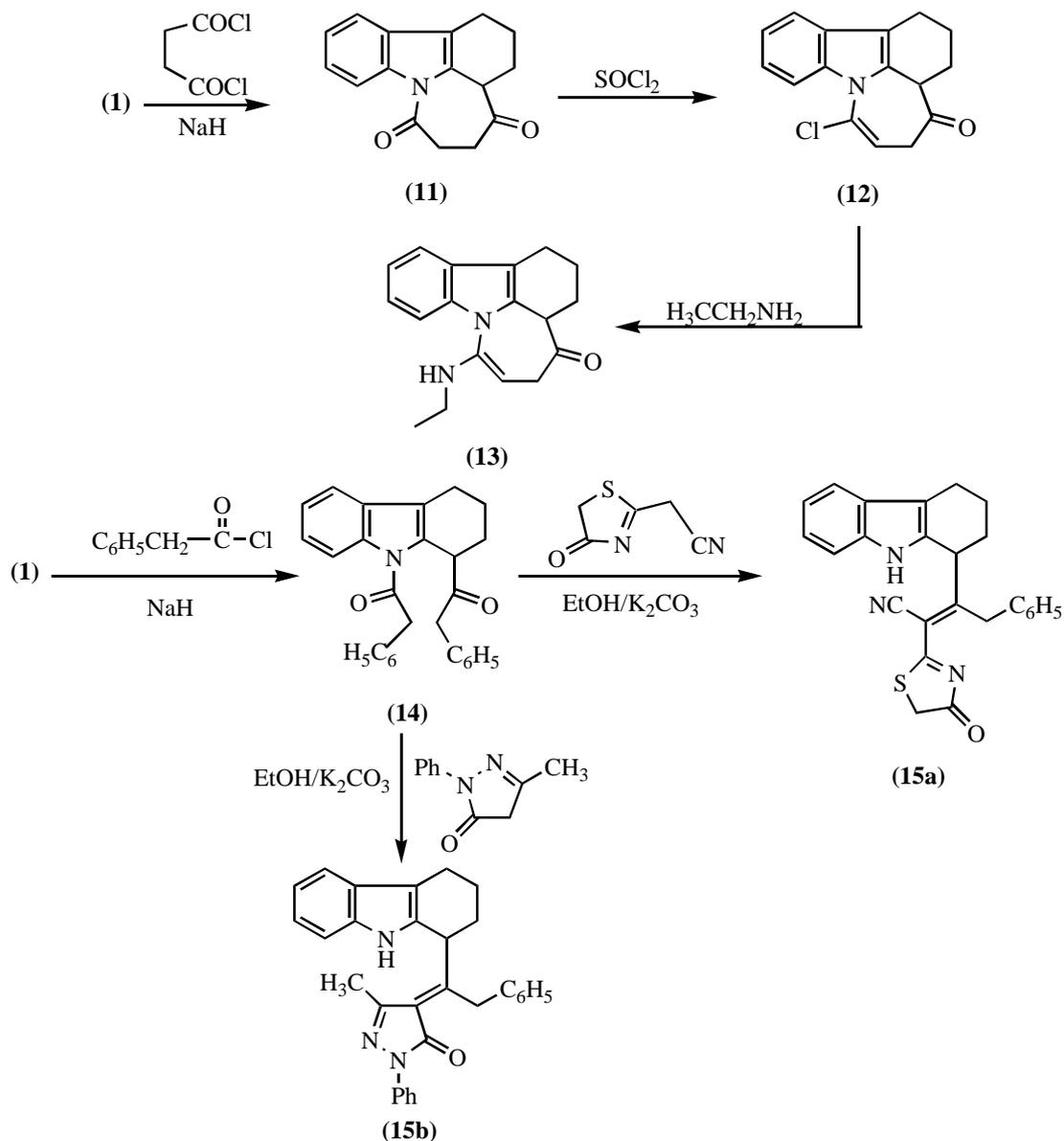
Furthermore, interaction of the imino derivative **3d** with ethyl cyanoacetate gave a product with analytical data indicating that one mole of ethanol was eliminated, followed by hydrolysis of the cyano and imino groups. This product was formulated as the monoamide of malonic acid derivative **8**. The structure of compound **8** was demonstrated on the basis of its elemental analysis and spectral data.

Condensation of acetyltetrahydrocarbazole **2** with pyridine-3-carboxaldehyde yielded the arylidine derivative **9**, which upon treatment with hydrazine hydrate in ethanol gave the pyrazole derivative **10**. The IR spectrum of **10** showed the complete disappearance of the CO band present in the parent compound.

Acylation of 1,2,3,4-tetrahydrocarbazole **1** with succinoyl chloride in presence of sodium hydride caused cyclization via elimination of two molecules of HCl to give the azepine derivative **11**. Chlorination of **11** with thionyl chloride afforded the corresponding chloroderivative **12**, which upon treatment with ethylamine furnished the corresponding ethylamino derivative **13**.

In contrast to the behaviour of **1** towards acetyl chloride and succinoyl chloride, the reaction of **1** with phenylacetyl chloride consumed two moles of the reagent to produce the 1,9-diphenylacetyl-tetrahydrocarbazole derivative **14**.

Compound **14** was reacted with some active methylene compounds such as 2-cyano-methylthiazolone [10] and a pyrazolone derivative. Reaction took place via condensation of the methylene group with the carbonyl group and hydrolysis of the 9-amide to give the corresponding thiazolo and pyrazolo derivatives **15a,b** (Scheme 2). The spectral data was all in agreement with the proposed structures.



Scheme 2

EXPERIMENTAL

General

All melting points are uncorrected. Microanalytical data were obtained at the Microanalytical Data Unit at Cairo University. IR spectra were recorded in KBr disks on a Unicam SP 200 spectrophotometer. $^1\text{H-NMR}$ spectra were measured on a Jeol DFF 100 (270 Mhz) with TMS as an internal reference. The mass spectra were recorded at Cairo University on a Shimadzu-GC-MS-QP 100 EX using the direct inlet system.

1-Acetyl-1,2,3,4-tetrahydro-9H-carbazole (2)

Acetyl chloride (0.1 mol) was added to 1,2,3,4-tetrahydro-9H-carbazole (**1**) (0.1 mole) dissolved in glacial acetic acid (10 mL) and the mixture was refluxed for half an hour. The solution was evaporated and the residue was crystallized to give the title compound (Table 1).

General procedure for the preparation of 1-(2,3,4,9)-Tetrahydro-1H-carbazol-1-yl)ethylidene thiourea (3a), 1-(2,3,4,9)-tetrahydro-1H-carbazol-1-yl)-ethylidene semicarbazone (3b), 1-(2,3,4,9)-tetrahydro-1H-carbazol-yl)-ethylidene thiosemicarbazone (3c) and 1-(2,3,4,9)-tetrahydro-1H-carbazol-1-yl)-ethylidene amino acetic acid (3e)

Compound **2** (0.01 mole) was dissolved in ethanol (20 mL), sodium hydroxide (10%; 10 mL) and thiourea, semicarbazide, thiosemicarbazide or glycine (0.01 mole) was added. The reaction mixture was refluxed for 4 hrs., cooled and dilute hydrochloric acid (10 mL) was added. The solid formed was filtered off and crystallized to furnish compounds **3a,b,c and e**, respectively (Table 1).

1`-[1-(2,3,4,9-Tetrahydrocarbazol-1-ylidene)-N-(thiazolidin-4-one)ethanamine (5)

Chloroacetic acid (0.01 mole) was added to a solution of **3a** (0.01 mole) in dry benzene (20 mL) containing a few drops of triethylamine. The reaction mixture was refluxed for 4 hr and left to cool. The precipitate formed was crystallized to give **5** (Table 1).

General procedure for the preparation of 3-methyl-2,4,5,6-tetrahydro[1,2,6]thiadiazino[4,3,2-jk]-carbazol-2-yl-2-thiourea-1-oxide (6) and 7-chloro-1,2,3,3a-tetrahydro-[3,2,1-jk]carbazol-4-one (12)

Thionyl chloride (0.05 mole) was added portionwise to a solution of **3c** or **11** (0.01 mole) in pyridine (20 mL) respectively. The reaction mixture was refluxed on a water bath for 30 minutes, excess solvent was evaporated and the resulting solid was washed with petroleum.ether (b.p. 60-80°C) and crystallized to furnish compounds **6** or **12** (Table 1).

3-Methyl-2,4,5,6-tetrahydro[1,2,6]thiadiazino[4,3,2jk]carbazol-2-yl amino-(thioxo)methylamino-methanone-1-oxide (7)

Ethyl formate (0.01 mol) was added to a solution of **6** (0.01 mol) in ethanol (20 mL) and hydrochloric acid (10%, 10 mL). The reaction mixture was refluxed for 4hr, left to cool and the solid was crystallized to give compound **7** (Table 1).

3-Oxo-3-[3-(1-2,3,4,9-pentahydrocarbazole-1-ylidene)-ethyl]ureidopropionic acid (8)

A mixture of compound **3d** (0.01 mol) and ethyl cyanoacetate (0.01 mol) in ethanol (25 mL) with 10 mL (10%) sodium hydroxide was refluxed for 4 hrs then cooled and neutralized with dilute hydrochloric acid. The solid thus formed was filtered off and crystallized to give **8** (Table 1).

3-Pyridin-3-yl-1-(2,3,4,9-tetrahydro-1-carbazol-1-yl)prop-2-en-1-one (9)

A mixture of **2** (0.01 mol) and pyridine 3-carbaldehyde (0.01 mol) in ethanol (20 mL) containing a few drops of piperidine was refluxed for 4 hrs. The product precipitated after cooling, was filtered off and crystallized to give compound **9** (Table 1).

1-(5-Pyridin-3-yl-1H-pyrazol-3-yl)2,3,4,9-tetrahydro-1H-carbazole (10)

A mixture of **9** (0.001 mol) and hydrazine hydrate (0.003 mol) in ethanol (20 mL) was refluxed for 3 hr, then left to cool. The solid was filtered off and crystallized to give **10** (Table 1).

7-Ethylamino-1,2,3,3a-tetrahydro[3,3,1-jk]carbazole-4-one (13)

Compound **12** (0.01 mol) was fused with ethylamine (0.012 mol) at 150°C for 30 min. The solid product that obtained after trituration with ethanol was filtered and crystallized to afford **13** (Table 1).

1,2,3,3a-Tetrahydroazepino[3,2,1-jk]carbazole-4,7-dione (11) and 1,9-diphenylacetyl-1,2,3,4-tetrahydrocarbazole (14)

Sodium hydride (0.04 mole) was added to compound **1** (0.01 mol) dissolved in dry dimethylformamide (75 mL) and the mixture was heated at 90°C for 1 hr., left to cool and a solution of succinoyl chloride or phenyl acetyl chloride (0.01 mole) in dry dimethyl formamide (20 mL) was added slowly to the mixture, which was then heated at 90°C for 4 hrs., left to cool and treated with ice. The precipitate formed was filtered off, washed with water, dried and crystallized to afford **11** or **14**, respectively (Table 1).

2(2,3,4,9-Tetrahydrocarbazol-1-yl)-1-cyano-1(5-hydro-4-oxo-1,3-thiazol-2-yl)-3-phenyl-1-propene (15a) and [1-(2,3,4,9-tetrahydrocarbazol-1-yl)-2-phenyl-1-[(3-methyl-1-phenyl)pyrazol-5-one-1-ylidene]ethane (15b)

A solution of **14** (0.001 mol) in ethanol (20 mL) was treated with 2-cyanomethyl thiazol-4-one or 3-methyl-1-phenylpyrazol-5-one (0.01 mol) in presence of anhydrous potassium carbonate (2 g). The reaction mixture was refluxed for 4 hr, left to cool and filtered. The precipitate so formed was crystallized to furnish compounds **15a,b** (Table 1).

Table 1: Physical and analytical data for synthesized compounds

Compd No.	M.P.* °C	Yield %	Formula (M. Wt)	Elemental analyses				
				Calculated/ Found, %				
				C	H	N	Cl	S
2	122 ^a	59	C ₁₄ H ₁₅ NO	78.87	7.04	6.57		
			(213)	78.77	7.10	6.49		
3a	190 ^b	60	C ₁₅ H ₁₇ N ₃ S	66.38	6.31	15.48		11.81
			(271.37)	66.21	6.11	15.32		11.71
3b	140 ^b	65	C ₁₅ H ₁₈ N ₄ O	66.64	6.71	20.72		
			(270.31)	66.51	6.66	20.63		
3c	160 ^b	62	C ₁₅ H ₁₈ N ₄ S	62.90	6.33	19.56		11.19
			(286.39)	62.81	6.25	19.46		11.09
3d	240 ^c	66	C ₁₅ H ₁₈ N ₄	70.83	7.13	22.03		
			(254.32)	70.71	7.03	21.97		
3e	170 ^b	50	C ₁₆ H ₁₈ N ₂ O ₂	70.03	6.66	10.36		
			(270.3)	71.00	6.57	10.42		
5	135 ^b	55	C ₁₇ H ₁₇ N ₃ OS	65.51	5.46	13.49		10.28
			(311.38)	65.49	5.50	13.38		10.26
6	180 ^b	57	C ₁₅ H ₁₆ N ₄ OS ₂	54.19	4.85	16.85		19.29
			(332.42)	54.01	4.69	16.72		19.15
7	220 ^c	50	C ₁₆ H ₁₆ N ₄ O ₂ S ₂	53.33	4.47	15.55		17.76
			(360.3)	53.29	4.39	15.44		17.66
8	190 ^b	64	C ₁₈ H ₁₉ N ₃ O ₄	63.33	5.61	12.31		
			(341.31)	63.11	5.51	12.08		
9	100 ^d	65	C ₂₀ H ₁₈ N ₂ O	79.44	6.00	9.26		
			(302.35)	79.31	5.95	9.16		
10	155 ^b	55	C ₂₀ H ₁₈ N ₄	76.43	5.73	17.83		
			(314)	76.26	5.71	17.88		
11	160 ^b	53	C ₁₆ H ₁₅ NO ₂	75.87	5.97	5.53		
			(253.26)	75.77	5.85	5.49		
12	210 ^b	63	C ₁₆ H ₁₄ NOCl	70.71	5.19	5.15	13.04	
			(271.72)	70.63	5.00	5.03	13.00	
13	140 ^b	69	C ₁₈ H ₂₀ N ₂ O	77.11	7.19	9.99		
			(280.34)	77.00	7.13	9.82		
14	180 ^b	50	C ₂₈ H ₂₅ NO ₂	82.53	6.18	3.44		
			(407.48)	82.39	6.08	3.34		

15a	100 ^e	61	C ₂₅ H ₂₁ N ₃ OS	72.98	5.15	10.21		
			(411.42)	72.82	5.09	10.12		
15b	160 ^b	57	C ₃₀ H ₂₇ N ₃ O	80.87	6.11	9.43		
			(445.52)	80.79	6.01	9.31		

* Recrystallization solvents: ^aMeOH, ^bEtOH, ^cDMF/H₂O, ^dbenzene, ^epetroleum. ether (b.p. 80-100°C).

Table 2: IR spectral data for the synthesized compounds

Compd. No.	$\nu_{\max.}/\text{cm}^{-1}$
2	3440 (NH), 2990 (CH-aliphatic), 1691 (C=O)
3a	3400, 3370, 3240 (NH, NH ₂), , 2890 (CH aliphatic), 1650 (C=N), 1340 (C=S)
3b	3430, 3310, 3250 (NH, NH ₂), 1680 (C=O), 1625 (C=N)
3c	3430, 3300, 3220 (NH, NH ₂), 1640 (C=N), 1342 (C=S)
3d	3450, 3320, 3200 (NH, NH ₂), 1620 (C=N)
3e	3400-2800 (br. NH + OH), 1705 (C=O), 1630 (C=N)
5	broad band around 3396 (2NH), 1688 (C=O), 1639 (C=N)
6	3340, 3300, 3200 (NH, NH ₂), 1340 (C=S)
7	3370, 3250 (2NH), 1660 (C=O), 1340 (C=S)
8	3500-2600 (NH + OH), 1710 (C=O, carboxylic), 1680 (C=O), 1650 (C=N)
9	3398 (NH), 2990 (CH-aliphatic), 1660 (C=O), 1640 (C=N)
10	3450, 3270 (2NH), 2890 (CH-aliphatic), 1640 (2C=N)
11	2985 (CH-aliphatic), 1720 (br. 2C=O)
12	2980 (CH-aliphatic), 1720 (C=O)
13	3410 (NH), 2990 (CH aliphatic), 1720 (C=O)
14	2985 (CH aliphatic), broad band around 1700 (2C=O)
15a	3415 (NH), 2220 (C≡N), 1680 (C=O), 1625 (C=N)
15b	3410 (NH), 1680 (C=O), 1635 (C=N)

Table 3: ¹H-NMR spectra for some of the synthesized compounds

Compd. No. (Solvent)	δ (ppm)
2 (CDCl ₃)	1.8-1.9 (m, 4H, 2CH ₂ -cyclo), 2.2-2.3 (m, 3H, CH ₂ + CH-cyclo), 2.8 (s, 3H, COCH ₃), 7.2-7.5 (m. 4H, Ar-H), 10.20 (s, 1H, NH; exchangeable)
3a (CDCl ₃)	1.8-1.9 (m, 4H, 2CH ₂ -cyclo), 2.2-2.4 (m, 3H, CH ₂ + CH-cyclo), 2.7 (s, 3H, CH ₃), 5.6 (s, 2H, NH ₂ ; exchangeable), 7.2-7.6 (m. 4H, Ar-H), 10.20 (s, 1H, NH; exchangeable)

3c (CDCl ₃)	1.8-1.9 (m, 4H, 2CH ₂ -cyclo), 2.2-2.4 (m, 3H, CH ₂ + CH-cyclo), 2.7 (s, 3H, CH ₃), 5.6 (s, 2H, NH ₂ ; exchangeable), 7.1-7.5 (m, 4H, Ar-H), 9.1 (s, 1H, NH, exchangeable), 10.25 (s, 1H, NH; exchangeable)
3e (CDCl ₃)	1.85-1.95 (m, 4H, 2CH ₂ -cyclo), 2.2-2.35 (m, 3H, CH ₂ + CH-cyclo), 3.7 (s, 2H, CH ₂), 7.2-7.45 (m, 4H, Ar-H), 10.2 (s, 1H, NH; exchangeable), 10.6 (s, 1H, OH, exchangeable)
5 (CDCl ₃)	1.75-1.9 (m, 4H, 2CH ₂ -cyclo), 2.2-2.3 (m, 2H, CH ₂ -cyclo), 2.7 (s, 3H, CH ₃), 3.9 (s, 2H, CH ₂), 6.9-7.4 (m, 4H, Ar-H), 9.2 (s, 1H, NH, thiazolidine; exchangeable), 10.2 (s, 1H, NH; exchangeable)
8 (CDCl ₃)	1.75-1.85 (m, 4H, 2CH ₂ -cyclo), 2.2-2.35 (m, 3H, CH ₂ + CH-cyclo), 2.6 (s, 3H, CH ₃), 4.6 (s, 2H, CH ₂), 6.85-7.3 (m, 4H, Ar-H), 9.1 (s, 1H, NH, exchangeable), 10.20 (s, 1H, NH; exchangeable), 10.6 (s, 1H, OH; exchangeable).
9 (CDCl ₃)	1.8-1.9 (m, 4H, 2CH ₂ -cyclo), 2.15-2.4 (m, 3H, CH ₂ + CH-cyclo), 6.8-7.3 (dd, 2H, H-olefinic), 7.4-8.3 (m, 8H, Ar-H), 10.2 (s, 1H, NH; exchangeable)
15b (DMSO-d ₆)	1.75-1.85 (m, 4H, 2CH ₂ -cyclo), 2.2-2.45 (m, 3H, CH ₂ + CH-cyclo), 3.0 (s, 3H, CH ₃), 3.9 (s, 2H, CH ₂), 7.2-7.6 (m, 14H, Ar-H), 10.2 (s, 1H, NH; exchangeable)

Table 4: Mass spectral data for some synthesized compounds

Compd. No.	m/e
3e	270 (M ⁺ , 1.0%), 255 (M-15 (CH ₃); 1.0%), 226 (M-44 (CO ₂); 1.5%), 211 (7.59 (CO ₂ + CH ₃); 5.7%), 191 (10.3%), 167 (16.9%), 149 (35.2%), 125 (20.2%), 111 (31.4%), 97 (13.6%), 57 (100%)
5	296 (M-15 (CH ₃); 0.5%), 247 (0.5%), 229 (0.5%), 167 (11.9%), 154 (3.9 %), 143 (100%), 127 (4.98%), 116 (3.16%), 115 (9.8%), 85 (7.45%), 77 (4.2%)
7	360 (M ⁺ , 1.0%), 344 (M-16 (O); 0.7%), 341 (0.5%), 269 (1.3%), 267 (2.64%), 235 (2.0 %), 217 (1.5%), 199 (11.86%), 170 (1.19%), 167 (41%), 154 (2.4%), 139 (8.6%), 127 (3.6%), 115 (7.4%), 105 (11.3%), 91 (17.2%), 77 (23.4%), 64 (100%)
8	341 (M ⁺ , 0.5%), 297 (M-44 (CO ₂); 0.5%), 278 (0.5%), 217 (0.5%), 187 (18.8%), 171 (89.2 %), 143 (100%), 115 (11.9%), 83 (5.9%), 77 (8.9%)
10	314 (M ⁺ , 0.5%), 299 (0.1%), 277 (0.3%), 261 (0.5%), 249 (1.0%), 230 (0.5 %), 215 (100%), 210 (0.5%), 191 (1.0%), 189 (1.0%), 171 (90.5%), 170 (26.86%), 143 (10.0%), 115 (13.49%), 77

	(5.6%)
11	253 (M ⁺ , 0.5%), 225 (M-28 (CO); 0.5%), 197 (M-56 (2CO); 0.5%), 184 (0.6%), 171 (10%), 159 (1.4 %), 145 (1.4%), 133 (1.6%), 115 (15.3%), 101 (89.8%), 74 (62.5%), 55 (100%)
12	271 (M ⁺ , 1.5%), 273 (M+2 (Cl isotope); 0.5%), 243 (M-28 (CO); 1.2%), 236 (M-35 (Cl), 1.2%), 213 (22.5%), 171 (66.5 %), 168 (38.3%), 143 (100%), 128 (24.3%), 115 (33.4%), 97 (24.2%)
13	280 (M ⁺ , 0.5%), 252 (M-28 (CO); 0.5%), 236 (M-44 (C ₂ H ₅ NH); 0.5%), 231(0.5%), 186 (0.5%), 150 (1.0 %), 128 (2.5%), 102 (66.8%), 94 (15%), 86 (100%), 84 (85.0%)
14	407 (M ⁺ , 0.7%), 288 (0.8%), 279 (33.1%), 255 (26.1%), 227 (11.3%), 209 (48.3%), 194 (58.6%), 167 (53.2%), 149(100%), 111 (18.8%), 97 (28.7%), 91 (65.9%), 77 (5.24%)
15a	411 (M ⁺ , 0.5%), 383 (M-28 (CO); 0.5%), 354 (1.16%), 310 (0.5%), 289 (4.6%), 236 (8.4 %), 200 (0.7%), 171 (8.2%), 140 (100%), 112 (10.4%), 91 (33.7%)

Pharmacological Study: Cytotoxic assay

The cytotoxicity assay performed using a microculture tetrazolium (MTT) sigma method [11]. The cultured cells at a long phase of their growth were treated in triplicate with various concentrations of chemical ranging from 0.5-100 µg/ mL. Synthesized compounds **2,3a, 3c, 6, 7, 14** and **15a** were dissolved in DMSO by adding 10 µL DMSO to each tested compound followed by gentle shaking. The cultured cells were then incubated for 18 hrs at 37°C in a humidified atmosphere of 5% CO₂. The cell concentration was determined by counting BT₂₀ cell in a hemocytometer. Results were expressed as the dose that inhibited 50% control growth after incubation period (ED₅₀) the value were estimated from a semilog plot of the drug concentration (µg/mL) VS the percent of viable cells (%), Table 5.

Table (5): Cytotoxic activity against breast cancer B₂₀

Compound No.	ED ₅₀
2	30
3a	42
3c	38
6	37
7	35
14	29
15a	26

The ranking of anticancer activity (Table 5) was found to be **15a**, **14**, **2**, **7**, **6**, **3c** and **3a** in descending order.

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