

Synthesis of some new 4,5-dihydro-6-(4-methoxy-3-methylphenyl)-3(2H)-pyridazinone derivatives

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Síntesis de algunos nuevos derivados de 4,5-dihidro-6-(4-metoxi-3-metilfenil)-3(2H)-piridazinona

Síntesi d'alguns nous derivats de 4,5-dihidro-6-(4-metoxi-3-metilfenil)-3(2H)-piridazinona

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RESUMEN

En el presente estudio se describe la síntesis de derivados de 4,5-dihidro-6-(4-metoxi-3-metilfenil)-3(2H)-piridazinona. La síntesis del primer compuesto objetivo, la 4,5-dihidro-6-(4-metoxi-3-metilfenil)-3(2H)-piridazinona (1), se consigue mediante acilación de Friedel-Crafts del *o*-cresil metil éter con anhídrido succínico y subsiguiente ciclación del *g*-cetoácido intermedio con hidrato de hidrazina. La condensación del compuesto 1 con aldehídos aromáticos en presencia de etóxido sódico rinde las correspondientes piridazinonas 4-bencilsubstituidas 3a-d. La piridazinona 1 experimenta deshidrogenación por tratamiento con una mezcla de bromo/ácido acético, dando 4. La piridazina 5 se sintetiza por reacción de la piridazinona 1 con 1,3-difenil-2-propen-1-ona mediante la reacción de adición de Michael. Los derivados *N*-dialquilaminometil 6a-b se obtienen a partir de la reacción de la piridazinona 1 con formaldehído y una amina secundaria, mientras que la reacción de 1 con formaldehído rinde el derivado *N*-hidroximetil 7. Este estudio también incluye la síntesis del derivado de 3-cloropiridazinona 8 con excelente rendimiento por calefacción de la piridazinona 3b en oxitricloruro de fósforo. También se estudia el comportamiento del derivado clorado mencionado frente a la azida sódica, la bencilamina y el ácido antranílico. Las estructuras propuestas para los productos se confirman mediante análisis elemental, datos espectroscópicos y evidencia química.

Palabras clave: piridazinona, cloropiridazina, quinazolinona, tetrazol, reacción de Michael, reacción de Mannich

SUMMARY

The present study describes the synthesis of 4,5-dihydro-6-(4-methoxy-3-methylphenyl)-3(2H)-pyridazinone derivatives. The synthesis of the first target compound, 4,5-dihydro-6-(4-methoxy-3-methylphenyl)-3(2H)-pyridazinone (1), was achieved by Friedel-Crafts acylation of *o*-cresyl

methyl ether with succinic anhydride and subsequent cyclization of the intermediary γ -keto acid with hydrazine hydrate. Condensation compound 1 with aromatic aldehydes in the presence of sodium ethoxide affords the corresponding 4-substituted benzyl pyridazinones (3a-d). The pyridazinone 1 underwent dehydrogenation upon treatment with bromine/acetic acid mixture to give (4). Pyridazine (5) has been synthesized upon the reaction of pyridazinone (1) with 1,3-diphenyl-2-propen-1-one under the Michael addition reaction. *N*-dialkylaminomethyl derivatives 6a-b have been obtained from the reaction of pyridazinone 1 with formaldehyde and secondary amine, whereas reaction of 1 with formaldehyde gives *N*-hydroxymethyl derivative (7). This study also includes the synthesis of the 3-chloro pyridazinone derivative 8 in excellent yield by heating pyridazinone 3b in phosphorus oxychloride. The behaviour of the chloro derivative toward sodium azide, benzyl amine and anthranilic acid was also studied. The proposed structures of the products were confirmed by elemental analysis, spectral data and chemical evidence.

Keywords: pyridazinone, chloropyridazine, quinazolinone, tetrazol, Michael reaction, Mannich reaction

RESUM

En el present estudi, es descriu la síntesi de derivats de 4,5-dihidro-6-(4-metoxi-3-metilfenil)-3(2H)-piridazinona. La síntesi del primer compost objectiu, la 4,5-dihidro-6-(4-metoxi-3-metilfenil)-3(2H)-piridazinona (1), s'assoleix mitjançant acilació de Friedel-Crafts de l'*o*-cresil metil éter amb anhídrid succínic i subseqüent ciclització del *g*-cetoàcid intermedi amb hidrat d'hidrazina. La condensació del compost 1 amb aldehids aromàtics en presència

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d'etòxid sòdic rendeix les corresponents piridazinones 4-benzilsubstituídes 3a-d. La piridazinona 1 experimenta deshidrogenació per tractament amb una mescla de brom/àcid acètic, donant 4. La piridazina 5 es sintetitza per reacció de la piridazinona 1 amb 1,3-difenil-2-propen-1-ona mitjançant la reacció d'addició de Michael. Els derivats N-dialquilaminometil 6a-b s'obtenen a partir de la reacció de la piridazinona 1 amb formaldehid i una amina secundària, mentre que la reacció d'1 amb formaldehid dona el derivat N-hidroximetil 7. Aquest estudi també inclou la síntesi del derivat de 3-cloropiridazinona 8 amb excel·lent rendiment per calefacció de la piridazinona 3b en oxitriclorur de fòsfor. També s'estudia el comportament del derivat clorat esmentat front a l'azida sòdica, la benzilamina i l'àcid antranílic. Les estructures proposades per als productes es confirmen mitjançant anàlisi elemental, dades espectroscòpiques i evidència química.

Mots clau: piridazinona, cloropiridazina, quinazolinona, tetrazole, reacció de Michael, reacció de Mannich

INTRODUCTION

The 3(2H)-pyridazinone derivatives, particularly those bearing an aryl group at position-6, have attracted considerable attention due to their characteristic pharmacological and biological activities. They are reported to exhibit antiplatelet [1-2], antihypertensive [3-4], antimicrobial [5] analgesic and anti-inflammatory activities [6], in addition they are known for their cardiovascular effects [7-8]. These activities promoted the synthesis of a large number of pyridazinone derivatives in order to explore the usefulness of this heterocyclic system. In the present study, various new pyridazinone derivatives have been synthesized.

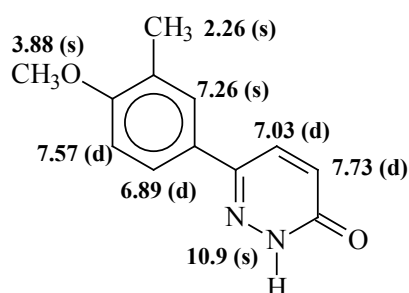
RESULTS AND DISCUSSION

β -Aroyl propionic acids have been successfully used in the synthesis of 6-aryl-3(2H)-pyridazinone by the reactions with hydrazines [9-10]. Various new pyridazinone derivatives have been synthesized according to the reaction sequences outlined in Schemes 1-2. The key compound, 4,5-dihydro-6-(4-methoxy-3-methylphenyl)-3(2H)-pyridazinone (**1**), was synthesized in good yield by Friedel-Crafts acylation of o-cresyl methyl ether with succinic anhydride [11] and subsequent cyclization of the inter-

mediate, 4-(4-methoxy-3-methylphenyl)-4-oxo-butanoic acid, with hydrazine hydrate in boiling ethanol.

The reaction of pyridazinone **1** with appropriate aromatic aldehydes in the presence of sodium ethoxide afforded the corresponding 4-substituted benzyl pyridazinones (**3a-d**) [12], which are the tautomers of 4-arylidene derivatives **2a-d**. The ^1H NMR of (**3c**) showed two singlets at δ 2.26 and 3.86 corresponding to methyl and methoxy groups, respectively. The singlet at δ 3.94 which attributed to the presence of methylene group at the position-4 of the pyridazine ring is an evidence of the formation of the tautomers **3**. The multiplets at δ 6.84-7.51 are indicative of the aromatic protons. The mass spectrum of (**3b**) exhibits two ion peaks at $m/z = 340$ and 342 corresponding to M^+ and M^++2 , respectively.

The pyridazinone **1** underwent dehydrogenation upon treatment with bromine/acetic acid mixture to give (**4**). The ^1H NMR of compound (**4**) showed two singlets at δ 2.28 and 3.89 corresponding to methyl and methoxy groups attached to benzene ring, respectively and the two doublets at δ 7.03 ($J = 9.85$) and 7.73 ($J = 9.75$) assigned to pyridazine protons H-5 and H-4, respectively. However, the singlet at δ 7.26 and the two doublets at δ 6.89 ($J = 8.23$) and 7.57 ($J = 9.80$) are corresponding to aromatic protons and finally the singlet at 10.9 is due to NH proton.

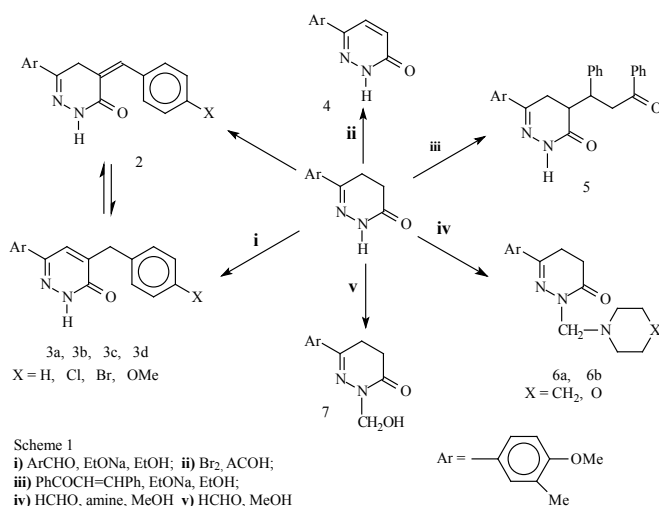


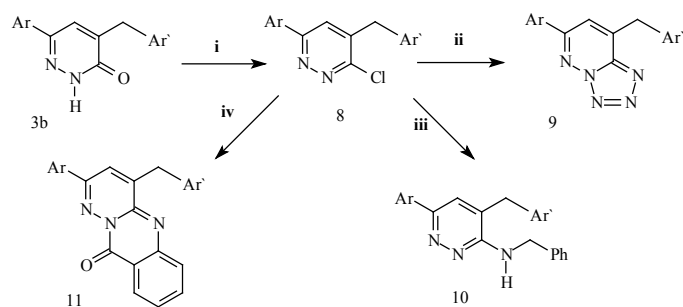
The reaction of pyridazinone (**1**) with 1,3-diphenyl-2-propen-1-one under the Michael reaction condition caused the addition of the methylene group at position-4 of pyridazinone **1** to the double bond of the chalcone with the formation of pyridazine (**5**).

The Mannich-reaction of the pyridazinone **1** occurred at position-2 and not at position-4. Thus, in the reaction of pyridazinone **1** with formaldehyde and secondary amine in methanol, the N-dialkylaminomethyl group attaches itself to the ring nitrogen with the formation of **6a-b**.

The N-hydroxymethyl derivative (**7**) was obtained via the interaction of pyridazinone **1** with formaldehyde [13].

On the other hand, the chloropyridazinone derivative **8** has also been used as the key starting material for the synthesis of some new heterocyclic compounds. The 3-chloro pyridazinone (**8**) was prepared in excellent yield by heating pyridazinone (**3b**) in phosphorus oxychloride. The IR spectrum of compound (**8**) showed the absence of absorption bands corresponding to NH and C=O groups. The tetrazole derivative (**9**) was prepared from (**8**) by refluxing with excess sodium azide in boiling dimethylformamide solution. Nucleophilic substitution of the chloro function in (**8**) with amines requires relatively harsh conditions by heating in a high boiling amine in solvent free condition. By this method, the benzylamino compound (**10**) could be obtained in good yield.





Scheme 2

i) POCl₃; ii) NaN₃, DMF; iii) PhCH₂NH₂; iv) anthranilic acid

Also, compound (**8**) was reacted with anthranilic acid, in DMF affording pyridazino[3,2-b]quinazolinone (**11**). Our attempts to convert the chloropyridazinone **8** to hydrazino derivative were failed under different conditions.

EXPERIMENTAL

All melting points reported are uncorrected and determined by the open capillary tube method using Gallen Kamp melting point apparatus. Microanalyses were carried out by the Micro Analytical Center at Cairo University. The IR spectra were recorded on FT/IR-460 plus spectrophotometers using KBr pellets. The ¹H NMR spectra were measured on Varian Gemini 300 MHz instrument with chemical shifts (δ) in ppm downfield from TMS. Mass spectra were recorded on Shomadzu GC-MS (QP-1000EX) instrument operating at 70eV. Homogeneity of all synthesized compounds was established by TLC Silica gel 60 F₂₅₄.

Synthesis of 4,5-dihydro-6-(4-methoxy-3-methylphenyl)-3(2H)-pyridazinone (**1**)

To a solution of 4-(4-methoxy-3-methylphenyl)-4-oxobutanoic acid (0.01 mole) in 20 ml ethanol, 1 ml of (80%) hydrazine hydrate was added. The reaction mixture was heated under reflux for 3 hrs. The solid product obtained after cooling was filtered off and crystallized from ethanol to give (**1**) as a white crystals. Yield: 73%; m.p. 152-153°C; IR (KBr) ν_{max} (cm⁻¹): 3200 (NH), 2923 (CH, aliphatic), 1659 (C=O); Anal. Calc. for C₁₂H₁₄N₂O₂ (218): C: 66.04, H: 6.47, N: 12.84. Found: C: 66.15, H: 6.41, N: 12.79.

Condensation of 4,5-dihydro-6-(4-methoxy-3-methylphenyl)-3(2H)-pyridazinone with aromatic aldehydes

To a solution of sodium ethoxide (prepared from 0.23 gm sodium and 30 ml absolute ethanol), pyridazinone (**1**) (0.01 mole) was added. The appropriate aldehyde (0.01 mole), namely benzaldehyde, p-chloro benzaldehyde, p-bromo benzaldehyde, and/or p-anisaldehyde, was added with stirring. The reaction mixture was kept overnight; the solid product obtained was filtered off and crystallized from the proper solvent.

4-benzyl-6-(4-methoxy-3-methylphenyl)-3(2H)-pyridazinone (3a) Yield: 61%; m.p. 200-202 °C; IR (KBr) ν_{max} (cm⁻¹): 3133 (NH), 2965 (CH, aliphatic), 1652 (C=O), 1604 (C=N); Anal. Calc. for C₁₉H₁₈N₂O₂ (306): C: 74.49, H: 5.92, N: 9.14. Found: C: 74.60, H: 6.70, N: 9.20.

4-(4-chlorobenzyl)-6-(4-methoxy-3-methylphenyl)-3(2H)-pyridazinone (3b) Yield: 76%; m.p. 210-212 °C; IR (KBr) ν_{max} (cm⁻¹): 3134 (NH), 2966 (CH, aliphatic), 1653 (C=O), 1606 (C=N); MS (m/z): 340- 342 (M⁺- M+2); Anal. Calc. for

C₁₉H₁₇ClN₂O₂ (340): C: 66.96, H: 5.03, N: 8.22. Found: C: 66.99, H: 5.08, N: 8.50.

4-(4-bromobenzyl)-6-(4-methoxy-3-methylphenyl)-3(2H)-pyridazinone (3c) Yield: 67%; m.p. 231-233 °C; IR (KBr) ν_{max} (cm⁻¹): 3117 (NH), 2956 (CH, aliphatic), 1659 (C=O), 1602 (C=N); ¹H NMR (CDCl₃) δ (ppm): 2.26 (s, 3H, CH₃), 3.86 (s, 3H, CH₃O), 3.94 (s, 2H, CH₂), 6.84-7.51 (m, 8H, Ar-H), 10.9-11 (s broad, 1H, N-H pyridazine); Anal. Calc. for C₁₉H₁₇BrN₂O₂ (385): C: 59.24, H: 4.45, N: 7.27. Found: C: 59.33, H: 4.50, N: 7.30.

4-(4-methoxybenzyl)-6-(4-methoxy-3-methylphenyl)-3(2H)-pyridazinone (3d) Yield: 60%; m.p. 184-185 °C; IR (KBr) ν_{max} (cm⁻¹): 3133 (N-H), 2957 (CH aliphatic), 1651 (C=O), 1604 (C=N); Anal. Calc. for C₂₀H₂₀N₂O₃ (336): C: 71.41, H: 5.99, N: 8.33. Found: C: 71.70, H: 6.05, N: 8.43.

Synthesis of 6-(4-methoxy-3-methylphenyl)-3(2H)-pyridazinone (**4**).

A stirred solution of pyridazinone (**1**) (0.01 mol) in glacial acetic acid (20 ml) was treated dropwise with bromine solution (0.012 mol in glacial acetic acid (10 ml)) at room temperature during 30 min. The solution was further stirred for 2 hrs, and then kept overnight. The precipitated product was filtered off, washed with ether and crystallized from ethanol to give (**4**). Yield: 56%; m.p. 240-242 °C; IR (KBr) ν_{max} (cm⁻¹): 2924 (CH, aliphatic), 1670 (C=O), 1588 (C=N); ¹H NMR (CDCl₃) δ (ppm): 2.28 (s, 3H, CH₃), 3.89 (s, 3H, CH₃O), 6.89 (d, 1H, H-5 pyridazinone, J=8.23), 7.15 (d, 1H, H-6 benzene ring, J=9.85), 7.27 (s, 1H, H-2 benzene ring), 7.57 (d, 1H, H-5 benzene ring J=9.80), 7.73 (d, 1H, H-4 pyridazinone J=9.75), 10.9 (s (broad), 1H, N-H pyridazine); Anal. Calc. for C₁₂H₁₂N₂O₂ (216): C: 66.65, H: 5.59, N: 12.95. Found: C: 66.87, H: 5.70, N: 13.89.

Synthesis of 4,5-dihydro-6-(4-methoxy-3-methylphenyl)-4-[3-oxo-1,3-diphenylpropyl]-3(2H)-pyridazinone (**5**)

To a solution of 0.01 mol pyridazinone (**1**) and potassium ethoxide (0.01 mol) in 30 mL absolute ethanol, 1,3-diphenyl propanone (0.01 mol) was added. The reaction mixture was heated under reflux for 4 hrs then left overnight at room temperature. The reaction mixture was acidified with dil. HCl. The solid product obtained was filtered off, washed with H₂O and crystallized from ethanol to give (**5**). Yield: 66 %; m.p. 190-191 °C; IR (KBr) ν_{max} (cm⁻¹): 3208 (NH), 2916 (CH aliphatic), 1674 (C=O), 1603 (C=N); ¹H NMR (CDCl₃) δ (ppm): 2.21 (s, 3H, CH₃), 2.64 (m, 1H, H-5 pyridazin), 2.84 (m, 1H, Ph-CH), 3.47 and 3.81 (2m, 2H, CO-CH₂), 3.67 (m, 1H, H-4, pyridazine) 3.86 (s, 3H, CH₃O), 6.75-7.89 (m, 13H, Ar-H), 8.66 (s, 1H, N-H pyridazine). Anal. Calc. for C₂₇H₂₆N₂O₃ (426): C: 76.03, H: 6.14, N: 6.57. Found: C: 76.24, H: 6.18, N: 6.68.

Synthesis of 2-[dialkylaminomethyl]-4,5-dihydro-6-(4-methoxy-3-methylphenyl)-3(2H)-pyridazinone (**6a-b**)

An aqueous solution of formaldehyde (3 ml, 35%) was added to a mixture of pyridazinone (**1**) (0.01 mole) and the appropriate secondary amine (0.02 mole) in ethanol, the reaction mixture was kept overnight at room temperature. The solid product obtained after dilution with water was filtered off and crystallized from the proper solvent to give **6a-b**.

2-[piperidinomethyl]-4,5-dihydro-6-(4-methoxy-3-methylphenyl)-3(2H)-pyridazinone (6a) Yield: 67%; m.p. 82-83 °C; IR (KBr) ν_{max} (cm⁻¹): 2927 (CH, aliphatic), 1678 (C=O), 1604 (C=N); ¹H NMR (CDCl₃) δ (ppm): 2.26(s, 3H,

CH₃), 2.51-2.54(t, 2H, H-5 pyridazine), 2.55-2.72 (m, 10H, piperidine), 2.91-2.96 (t, 2H, H-4 pyridazine), 3.87(s, 3H, CH₃O), 4.79 (s, 2H, N-CH₂-N) 6.84-7.57(m, 3H, Ar-H). Anal. Calc. for C₁₈H₂₅N₃O₂ (315): C: 68.54, H: 7.99, N: 13.32. Found: C: 68.64, H: 8.09, N: 13.36.

2-[morpholinomethyl]-4,5-dihydro-6-(4-methoxy-3-methylphenyl)-3(2H)-pyridazinone (6b) Yield: 53%; m.p. 152- 154 °C; IR (KBr) $\nu_{\max}$ (cm⁻¹): 2925 (CH, aliphatic), 1675 (C=O), 1605 (C=N). Anal. Calc. for C₁₇H₂₃N₃O₃ (317): C: 64.33, H: 7.30, N: 13.24. Found: C: 65.03, H: 7.35, N: 13.30.

Synthesis of 2-[hydroxymethyl]-4,5-dihydro-6-(4-methoxy-3-methylphenyl)-3(2H)-pyridazinone (7)

A mixture of (0.01 mole) pyridazinone **1**, aqueous formaldehyde (10 ml, 35%) and 20 ml water was refluxed for 4hrs. The solid product obtained after cooling was filtered off and crystallized from ethanol to give **7** as a white crystals. Yield: 81%; m.p. 171-173 °C; IR (KBr) $\nu_{\max}$ (cm⁻¹): 3315 (OH), 2963 (CH aliphatic), 1642 (C=O); ¹H NMR (CDCl₃) δ (ppm): 2.25 (s, 3H, CH₃), 2.56-2.63 (t, 2H, H-5 pyridazine), 2.92-2.95 (t, 2H, H-4 pyridazine), 3.86 (s, 3H, CH₃O), 5.29 (s, 2H, N-CH₂-O), 6.82-7.61(m, 3H, Ar-H). Anal. Calc. for C₁₃H₁₆N₂O₃ (248): C: 62.89, H: 6.50, N: 11.28. Found: C: 62.86, H: 6.48, N: 11.20.

Synthesis of 3-chloro-4-(4-chlorobenzyl)-6-(4-methoxy-3-methylphenyl)-pyridazine (8)

A suspension of **3b** (2 gm) in phosphorus oxychloride (20 ml) was refluxed for 4 hrs on a water bath at 70 °C. The reaction mixture, after cooling, was poured gradually into a mixture of crushed ice and sodium bicarbonate. The solid product obtained was collected by filtration and crystallized from ethanol to give **8** as colorless crystals, yield: 93%; m.p. 122- 124 °C; IR (KBr) $\nu_{\max}$ (cm⁻¹): 2923 (CH aliphatic), 1603 (C=N). ¹H-NMR (CDCl₃) δ (ppm): 2.28 (s, 3H, CH₃), 3.89 (s, 3H, CH₃O), 4.11 (s, 2H, CH₂), 6.90-7.80 (m, 8H, Ar-H). Anal. Calcd. for C₁₉H₁₆Cl₂N₂O (359): C: 63.52, H: 4.49, N: 7.80. Found: C: 63.50, H: 4.40, N: 7.78.

Synthesis of 8-(4-Chlorobenzyl)-6-(4-methoxy-3-methylphenyl)-tetrazolo[1,5-b]pyridazine (9)

To a solution of the chloro compound **8** (1 mmole) in DMF (10 mL) was added sodium azide (3 mmol), and the mixture was refluxed for 24 hrs. the product was collected by filtration and recrystallized from DMF to give **9** as colorless crystals, yield: 53%; m.p. 190-192 °C (decomp); IR (KBr) $\nu_{\max}$: 2923 (CH aliphatic), 1603 (C=N); ¹H-NMR (CDCl₃) δ (ppm): 2.30 (s, 3H, CH₃), 3.91 (s, 3H, CH₃O), 4.49 (s, 2H, CH₂), 6.92-7.89 (m, 8H, Ar-H). Anal. Calc. for C₁₉H₁₆ClN₅O (365): C: 62.38, H: 4.41, N: 19.14. Found: C: 62.30, H: 4.41, N: 19.10.

Synthesis of 3-benzylamino-4-(4-chlorobenzyl)-6-(4-methoxy-3-methylphenyl)-pyridazine (10)

A mixture of the chloro compound **8** (1 mmol) and benzylamine (2 mmol) was heated on oil bath for 6 hrs and the residue was triturated with diethyl ether, followed by crystallization from ethanol to give **10** as buff powder, yield: 53 %; m.p.169-170 °C; IR (KBr) $\nu_{\max}$ (cm⁻¹): 3426 (NH), 2950 (CH aliphatic), 1604 (C=N);. Anal. Calc. for C₂₅H₂₂ClN₃O (415): C: 72.19, H: 5.33, N: 10.10. Found: C: 72.13, H: 5.30, N: 10.10.

Synthesis of 4-(4-chlorobenzyl)-2-(4-methoxy-3-methylphenyl)-10-oxo-pyridazino[3,2-b]quinazoline (11)

A mixture of the chloro compound **8** (1 mmol) and anthranilic acid (2 mmol) was heated in an oil bath for 4 hrs, the solid product was collected and crystallized from ethanol to give compound **11** as colorless crystals, yield: 66 %; m.p.202-204 °C; IR (KBr) $\nu_{\max}$ (cm⁻¹): 2902 (CH aliphatic), 1651 (C=O) 1606 (C=N); ¹H-NMR (CDCl₃) δ (ppm): 2.24 (s, 3H, CH₃), 3.86 (s, 3H, CH₃O), 3.99 (s, 2H, CH₂), 6.84-7.50 (m, 12H, Ar-H);. Anal. Calc. for C₂₆H₂₀ClN₃O₂ (441): C: 70.67, H: 4.56, N: 9.51. Found: C: 70.49, H: 4.50, N: 9.47.

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