HETEROCYCLES, Vol. 75, No. 6, 2008, pp. 1479 - 1488. © The Japan Institute of Heterocyclic Chemistry
Received, 18th December, 2007, Accepted, 8th February, 2008, Published online, 15th February, 2008. COM-07-11311

A CONVENIENT SYNTHESIS OF NOVEL SERIES OF 4-CYCLOHEXYL-2-SUBSTITUTED [1,2,4]TRIAZOLO[1,5-*a*]QUINAZOLIN-5(4*H*)-ONES. NOVEL ISOMERS OF H_1 ANTIHISTAMINIC ACTIVITE AGENTS

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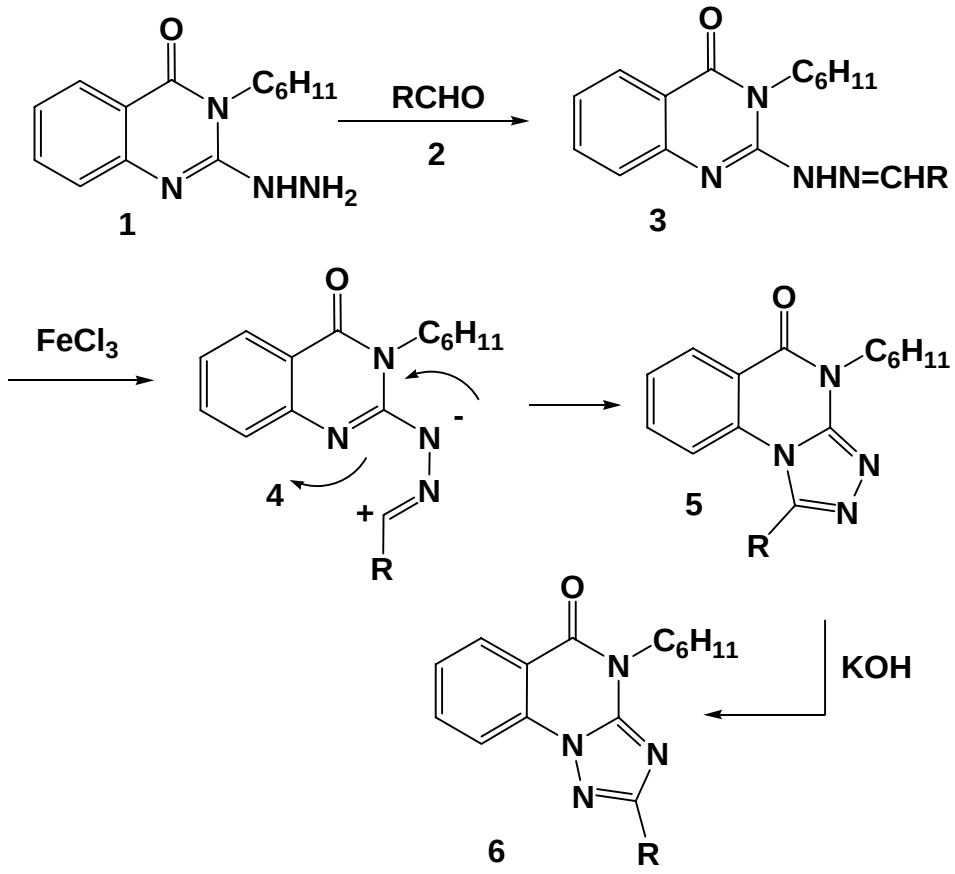
Abstract – A novel series of 2,4-disubstituted-1,2,4-triazolo[1,5-*a*]-quinazolin-5(4*H*)-ones were prepared by Dimroth rearrangement of their respective isomers namely 1,4-disubstituted[1,2,4]triazolo[4,3-*a*]-quinazolin-5(4*H*)-ones. The latter were prepared *via* new synthetic strategy based on 1,5-elecrocyclization of the respective *N*-(4-oxo-3-cyclohexylquinazolin-2-yl)nitrilimines.

INTRODUCTION

Literature survey reveals that several quinazolines and condensed quinazoline derivatives exhibit excellent antihistaminic activity.[1-3] For example, 1-substituted-4-cyclohexyl[1,2,4]triazolo[4,3-*a*]-quinazolin-5(4*H*)-ones having alkyl/alicyclic amine substitution at position 1 were reported recently to protect guina-pigs from histamine induced broncospasm significantly.[4] In view of this finding, it was interesting to explore the antihistaminic activity of the isomers of such compounds namely the title compounds. A literature survey reveals, however, that the target title compounds have not been reported hitherto and that the only method for synthesis of such ring system depends on the reaction of 2-hydrazinobenzoic acid with *N*-cyanoimidates.[5] Thus, to achieve our objective, it was necessary to develop a new convenient and general method for synthesis of the title compounds prior exploring their biological activity. In continuation of our ongoing studies dealing with the chemistry of nitrilimines and their precursors,[6-10] we wish to report herein the synthesis of the title compounds *via* a novel innovative route (Scheme 1). This route involves 1,5-electrocyclization of *N*-(4-oxo-3-cyclohexylquinazolin-2-yl) nitrilimines **4** (Scheme 1), generated *in situ* by oxidation of the respective hydrazones **3** and subjecting the resulting 1,2,4- triazolo[4,3-*a*]quinazolines **5** to Dimroth rearrangement to give the title compounds **6**.

This adopted strategy for synthesis of the intermediate 1,2,4-triazolo[4,3-*a*]quinazolines **5** seems to be of more applicability than the one reported in literature which depends on the cyclization of 2-hydrazino-3-substituted-quinazolin-4(3*H*)-ones with various one carbon donors.[11, 12]



R : a, C_6H_5; b, 4-MeC_6H_4; c, 4-ClC_6H_4; d, 4-$MeOC_6H_4$; e, 4-$O_2NC_6H_4$; f, 1-naphthyl; g, 2-furyl; h, 2-thienyl

Scheme 1

RESULTS AND DISCUSSION

The key starting aldehyde *N*-(3-cyclohexyl-3,4-dihydro-4-oxoquinazolin-2-yl)hydrazones **3** which have not been reported hitherto, were prepared in this study by refluxing 2-hydrazino-3-cyclohexylquinazolin-4(3*H*)-one **1** with the appropriate aldehydes **2** in ethanol in the presence of acetic acid as a catalyst (Scheme 1). The structures of these new hydrazones were evidenced by their elemental analyses and spectral (MS, IR and ^{1}H NMR) data (see Experimental). For example, their ^{1}H NMR in $CDCl_3$ revealed, in each case, three characteristic signals in the regions δ 1.2 - 2.7, 8.2 - 8.5 and 9.2 - 9.5 corresponding to the cyclohexyl, –N=CH- and hydrazone –NH-N=C protons, respectively.

When each of the hydrazones **3** was treated with equivalent amount of iron(III) chloride in ethanol for 30 min., it furnished, in each case, one crystalline product as evidenced by tlc analysis. The isolated products proved to be the respective 4-cyclohexyl-1-substituted-[1,2,4]triazolo[4,3-*a*]quinazolin-5(4*H*)-ones **5** (Scheme 1). Their structures were confirmed by their elemental analyses and mass spectra. For example, both elemental analysis and mass spectrum of each compound revealed that it has two hydrogens less than the respective hydrazone **3**. Also, their ^{1}H NMR spectra showed the absence of the –N=CH- and hydrazone –NH-N=C proton signals. Their IR spectra showed a carbonyl (C=O) absorption band near 1680 cm^{-1}. Their mass spectra showed two common peaks at m/z 227 and 145 assignable to 3-cyclohexylquinazoline cation and quinazolin-4-one moiety, respectively. The conversion of **3** into **5** is considered to result from 1,5-electrocyclization of the initially formed nitrilimines **4** (Scheme 1). This suggested pathway is reminiscent of other related oxidative cyclization of aldehyde N-heteroarylhydrazones with iron(III) chloride, which was reported to proceed *via* generation of the respective nitrilimines **4** which undergo *in situ* 1,5-electrocyclization to give the respective fused heterocycles.[13,14]

Next, Dimroth rearrangement[15-19] of 4-cyclohexyl-1-substituted[1,2,4]triazolo[4,3-*a*]quinazolin-5(4*H*)-ones **5** was examined. In our hands, treatment of **5** with potassium hydroxide in refluxing ethanol yielded, in each case one product that was identified as the respective [1,2,4]triazolo[1,5-*a*]quinazolin-5(4*H*)-one **6** (Scheme 1). The structures assigned to the latter isolated products **6** were consistent with their analytical and spectral MS, ^{1}H NMR, IR) data (see Experimental). The conversion of **5** into **6** is analogous to rearrangement of 1,2,4-triazolo[4,3-*a*]pyrimidines in alkali to the isomeric 1,2,4-triazolo-[1,5-*a*]pyrimidines.[15-19]

In conclusion, we have developed a general convenient method for synthesis of 1,4-disubstituted[1,2,4]triazolo[4,3-*a*]quinazolin-5(4*H*)-ones **5** and their isomers namely 2,4-disubstituted-[1,2,4]triazolo[1,5-*a*]quinazolin-5(4*H*)-ones **6**. The synthesized compounds together with their acyclo C-nucleosides are under evaluation for in vivo antihistaminic and sedative-hypnotic activities and the results will be published in due course. Our current studies are directed to extend the scope of the presented method to cover additional heterocyclic systems.

EXPERIMENTAL

All melting points were determined on an electrothermal Gallenkamp apparatus and are uncorrected. The IR spectra were measured on a Pye-Unicam SP300 instrument in potassium bromide discs. The ^{1}H-NMR spectra were recorded on a Varian Mercury VXR-300 spectrometer (300 MHz) in $CDCl_3$ or DMSO. The mass spectra were recorded on a GCMS-Q1000-EX Shimadzu and GCMS 5988-A HP spectrometers, the ionizing voltage was 70 eV. Elemental analyses were carried out by the Microanalytical Center of Cairo

University, Giza, Egypt. The starting 3-cyclohexyl-2-hydrazino-quinazolin-4(3*H*)-one (**1**) was prepared by hydrazinolysis of 3-cyclohexyl-2-thioxo-quinazoline-4(1*H*,3*H*)-one according to literature method.[20]

Aldehyde N-(3- cyclohexyl -3,4-dihydro-4-oxoquinazolin-2-yl)hydrazones (**3a-h**):

General Procedure. - To a mixture of 2-hydrazino-3-cyclohexylquinazolin-4(3*H*)-one **1** (1.3 g, 5 mmol) and the appropriate aldehyde **2** (5 mmol) in EtOH (50 mL), a few drops of acetic acid were added and the reaction mixture was refluxed for 3 h and then cooled. The reaction mixture was poured on ice-water. The precipitate formed was filtered off, washed with water then ethanol and finally crystallized from an appropriate solvent to give the corresponding hydrazone derivative **3**. The various hydrazone derivatives **3a-h** prepared are listed below together with their physical constants and spectral data.

Benzaldehyde N-(3-cyclohexyl-3,4-dihydro-4-oxoquinazolin-2-yl)hydrazone (**3a**): yellow crystals (yield 91%), mp 230 ^{o}C (EtOH-dioxane), IR (KBr) ν 3263 (-NH-), 1651 (C=O), 1615 (C=N) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 1.3-2.7 (m, 10H, cyclohexyl), 5.1 (m, 1H, CH-N, cyclohexyl), 6.9 – 8.1 (m, 9 H, ArH), 8.5 (s, 1H, N=CH), 9.3 (s, 1H, NH). MS m/z (%): 348 (M^++2, 5), 347 (M^+ +1, 5), 346 (M^+, 18), 277 (12), 265 (100), 263 (18), 250 (18), 227 (2), 187 (28), 161 (25), 145 (15), 119 (20), 90 (19), 89 (7), 77 (7). Anal. Calcd for $C_{21}H_{22}N_4O$ (346.44): C, 72.81; H, 6.40; N, 16.17. Found: C, 72.78; H, 6.35; N, 16.02 %.

4-Tolaldehyde N-(3-cyclohexyl-3,4-dihydro-4-oxoquinazolin-2-yl)hydrazone (**3b**): yellow crystals (yield 88%), mp 235 ^{o}C (EtOH-dioxane). IR (KBr) ν 3299 (-NH-), 1652 (C=O), 1614 (C=N). ^{1}H NMR ($CDCl_3$): δ 1.3-2.7 (m, 10H, cyclohexyl), 2.4 (s, 3H, CH_3), 5.1 (m, 1H, CH-N, cyclohexyl), 6.9 – 8.0 (m, 8 H, ArH), 8.4 (s, 1H, N=CH), 9.3 (s, 1H, NH). MS: m/z (%) 362 (M^++2, 10), 361 (M^++1, 25), 360 (M^+, 32), 279 (100), 280 (24), 264 (19), 234 (7), 200 (19), 187 (41), 161 (72), 145 (22), 119 (31), 104 (18), 90 (20), 79 (8). 77 (11). Anal. Calcd for $C_{22}H_{24}N_4O$ (360.45): C, 73.31; H, 6.71; N, 15.54. Found: C, 73.24; H, 6.67; N, 15.14 %.

4-Chlorobenzaldehyde N-(3-cyclohexyl-3,4-dihydro-4-oxoquinazolin-2-yl)hydrazone (**3c**): yellow crystals (yield 92%), mp 262 ^{o}C (EtOH-dioxane). IR (KBr) ν 3284 (-NH-), 1655 (C=O), 1616 (C=N) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 1.3-2.7 (m, 10H, cyclohexyl), 5.1 (m, 1H, CH-N, cyclohexyl), 6.9 – 8.1 (m, 8 H, ArH), 8.4 (s, 1H, N=CH), 9.2 (s, 1H, NH). . MS: m/z (%):382 (M^++2, 8), 381 (M^++1, 6), 380 (M^+, 18), 299 (100), 284 (13), 227 (1), 220 (15), 187 (27), 161 (42), 145 (20), 120 (11), 119 (31), 90 (16), 77 (6). Anal. Calcd for $C_{21}H_{21}ClN_4O$ (380.87): C, 66.22; H, 5.56; N, 14.71. Found: C, 66.28; H, 5.67; N, 14.59 %.

4-Methoxybenzaldehyde-N-(3-cyclohexyl-3,4-dihydro-4-oxoquinazolin-2-yl)hydrazone (**3d**): yellow-green crystals (yield 93%), mp 208 °C (EtOH-dioxane), IR (KBr) ν 3294 (-NH-), 1659 (C=O), 1617 (C=N).cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 1.3-2.7 (m, 10H, cyclohexyl), 3.8 (s, 3H, CH_3), 5.1 (m, 1H, CH-N, cyclohexyl), 6.9 – 8.0 (m, 8 H, ArH), 8.4 (s, 1H, N=CH), 9.3 (s, 1H, NH). MS: m/z (%) 378 (M^++2, 4), 377 (M^++1, 17), 376 (M^+, 36), 295 (61), 280 (23), 242 (11), 216 (25), 161 (100), 145 (17), 119 (31), 91 (23), 77 (14). Anal. Calcd for $C_{22}H_{24}N_4O_2$ (376.45): C, 70.19; H, 6.43; N, 14.88. Found: C, 70.28; H, 6.33; N, 14.76 %.

4-Nitrobenzaldehyde N-(3-cyclohexyl-3,4-dihydro-4-oxoquinazolin-2-yl)-hydrazone (**3e**): orange crystals (yield 91%), mp 270 °C (EtOH-DMF). IR (KBr) ν 3339 (-NH-), 1680 (C=O), 1621 (C=N) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 1.2-2.7 (m, 10H, cyclohexyl), 5.1 (m, 1H, CH-N, cyclohexyl), 7.0 – 8.3 (m, 8 H, ArH), 8.5 (s, 1H, N=CH), 9.3 (s, 1H, NH). MS: m/z (%) 393 (M^++2, 3), 392 (M^++1, 2), 391 (M^+, 9), 310 (100), 231 (18), 227 (1), 187 (27), 161 (26), 145 (19), 119 (24), 90 (14), 77 (5). Anal. Calcd for $C_{21}H_{21}N_5O_3$ (391.42): C, 64.44; H, 5.41; N, 17.89. Found: C, 64.34; H, 5.25; N, 17.75 %.

1-Naphthaldehyde N-(3-cyclohexyl-3,4-dihydro-4-oxoquinazolin-2-yl)hydrazone (**3f**): yellow crystals (yield 92%), mp 163 °C (EtOH-dioxane). IR (KBr) ν 3279 (-NH-), 1664 (C=O), 1617 (C=N) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 1.4-2.7 (m, 10H, cyclohexyl), 5.2 (m, 1H, CH-N, cyclohexyl) 6.9 – 8.6 (m, 11 H, ArH), 9.2 (s, 1H, N=CH), 9.3 (s, 1H, NH). MS: m/z (%) 397 (M^++1, 19), 396 (M+, 37), 315 (100), 300 (12), 242 (18), 187 (29), 162 (29), 154 (21), 145 (28), 127 (23), 119 (29), 90 (24), 77 (12). Anal. Calcd for $C_{25}H_{24}N_4O$ (396.48): C, 75.73; H, 6.10; N, 14.13. Found: C, 75.77; H, 6.08; N, 13.95 %.

2-Furfuraldehyde N-(3-cyclohexyl-3,4-dihydro-4-oxoquinazolin-2-yl)hydrazone (**3g**): yellow crystals (yield 90%), mp 197 °C (EtOH). IR (KBr) ν 3249 (-NH-), 1656 (C=O), 1614 (C=N) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 1.3-2.7 (m, 10H, cyclohexyl), 5.2 (m, 1H, CH-N, cyclohexyl) 6.5 – 8.0 (m, 7 H, ArH), 8.3 (s, 1H, N=CH), 9.3 (s, 1H, NH). MS: m/z (%): 337 (M^++1, 17), 336 (M^+, 29), 255 (100), 240 (33), 227 (7), 197 (20), 187 (19), 161 (90), 145 (24), 119 (46), 117 (10), 90 (38), 77 (7). Anal. Calcd for $C_{19}H_{20}N_4O_2$ (336.39): C, 67.84; H, 5.99; N, 16.65. Found: C, 67.64; H, 5.60; N, 16.47 %.

2-Thiophenealdehyde N-(3-cyclohexyl-3,4-dihydro-4-oxoquinazolin-2-yl)hydrazone (**3h**): pale yellow crystals (yield 92%), mp 132 °C (EtOH). IR (KBr) ν 3248 (-NH-), 1682 (C=O), 1616 (C=N)cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 1.3-2.7 (m, 10H, cyclohexyl), 5.3 (m, 1H, CH-N, cyclohexyl) 6.9 – 8.0 (m, 7 H, ArH), 8.5 (s, 1H, N=CH), 9.5 (s, 1H, NH). MS: m/z (%): 354 (M^++2, 5), 353 (M^++1, 16) 352 (M^+, 30), 271

(100), 256 (27), 241 (17), 192 (40), 187 (26), 161 (80), 145 (14), 119 (38), 96 (25), 90 (20), 81 (10), 77 (13). Anal. Calcd for $C_{19}H_{20}N_4OS$ (352.45): C, 64.75; H, 5.72; N, 15.90. Found: C, 64.63; H, 6.06; N, 15.71 %.

4-Cyclohexyl-1-substituted[1,2,4]triazolo[4,3-a]quinazolin-5(4H)-ones (**5a-h**):

General procedure: To a solution of each of the appropriate hydrazone **3** (2.5 mmol) in EtOH (50 mL) was added a solution of ferric chloride (2 M, 2 mL) and the mixture was refluxed for 30 min, then left overnight at rt, water was added to it. The solid that precipitated was filtered off, washed with water, dried and finally recrystallized from appropriate solvent to give the respective1,4-substituted[1,2,4]-triazolo- [1,5-*a*]quinazolin-5(4*H*)-one **5**. The compounds prepared together with their physical constants and spectral data are listed below.

4-Cyclohexyl-1-phenyl[1,2,4]triazolo[4,3-a]quinazolin-5(4H)-one (**5a**): white crystals (yield 82%), mp 175 ^oC (EtOH-water),. IR (KBr) ν 1690 (C=O), 1608 (C=N) cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.4-2.8 (m, 10H, cyclohexyl), 5.2 (m, 1H, CH-N, cyclohexyl) 7.1 – 8.4 (m, 9 H, ArH). MS: m/z (%): 345 (M^++1, 1), 344 (M^+, 8), 343 (13), 264 (24), 263 (100), 261 (58), 227 (7), 145 (6), 119 (5), 104 (8), 90 (7), 77 (5). Anal. Calcd for $C_{21}H_{20}N_4O$ (344.41) : C, 73.23; H, 5.85; N, 16.27. Found: C, 73.17; H, 5.78; N, 16.12 %.

4-Cyclohexyl-1-(4-tolyl)[1,2,4]triazolo[4,3-a]quinazolin-5(4H)-one (**5b**): pale yellow crystals (yield 85%), mp 234 ^oC (EtOH). IR (KBr) ν 1696 (C=O), 1610 (C=N) cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.4-2.8 (m, 10H, cyclohexyl), 2.5 (s, 3H, CH_3), 5.2 (m, 1H, CH-N, cyclohexyl) 7.2 – 8.4 (m, 8 H, ArH). MS: m/z (%): 360 (M^++2, 2), 359 (M^++1, 2), 358 (M^+, 5), 277 (100), 275 (69), 227 (2), 219 (3), 192 (4), 160 (3), 145 (5), 133 (5), 117 (5), 104 (10), 90 (12), 77 (6). Anal. Calcd for $C_{22}H_{22}N_4O$ (358.44): C, 73.72; H, 6.19; N, 15.63. Found: C, 73.61; H, 6.05; N, 15.50 %.

4-Cyclohexyl-1-(4-chlorophenyl)[1,2,4]triazolo[4,3-a]quinazolin-5(4H)-one (**5c**): white yellow crystals (yield 83%), mp 266 ^oC (EtOH-dioxane). IR (KBr) ν 1700 (C=O), 1610 (C=N) cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.4-2.8 (m, 10H, cyclohexyl), 5.2 (m, 1H, CH-N, cyclohexyl) 7.1 – 8.4 (m, 8 H, ArH). MS: m/z (%): 380 (M^++2, 2), 379 (M^++1, 3) 378 (M^+, 3), 297 (100), 295 (37), 227 (2), 213 (2), 160 (3), 145 (4), 104 (8), 77 (4). Anal. Calcd for $C_{21}H_{19}ClN_4O$ (378.85): C, 66.58; H, 5.05; N, 14.79. Found: C, 66.49; H, 5.25; N, 14.56 %.

4-Cyclohexyl-1-(p-methoxyphenyl)[1,2,4]triazolo[4,3-a]quinazolin-5(4H)-one (**5d**): white yellow crystals (yield 82%), mp 204 ^oC (EtOH),. IR (KBr) ν 1694 (C=O), 1613 (C=N) cm^{-1}. ^1H NMR

($CDCl_3$): δ 1.3-2.8 (m, 10H, cyclohexyl), 3.9 (s, 3H, CH_3), 5.2 (m, 1H, CH-N, cyclohexyl) 7.0 – 8.4 (m, 8 H, ArH).MS: m/z (%) : 375 (M^++1, 4), 374 (M^+, 9), 293 (100), 248 (11), 227 (3), 209 (4), 192 (6), 144 (3), 133 (13), 120 (5), 90 (19), 77 (8). Anal. Calcd for $C_{22}H_{22}N_4O_2$ (374.44): C, 70.57; H, 5.92; N, 14.96. Found: C, 70.29; H, 5.74; N, 14.81 %.

4-Cyclohexyl-1-(4-nitrophenyl)[1,2,4]triazolo[4,3-a]quinazolin-5(4H)-one (**5e**): white crystals (yield 85%), mp 275 °C (EtOH-dioxane). IR (KBr) ν 1671 (C=O), 1606 (C=N) cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.3-2.8 (m, 10H, cyclohexyl), 5.2 (m, 1H, CH-N, cyclohexyl) 7.1 – 8.5 (m, 8 H, ArH). MS: m/z (%):391 (M^++2, 3), 390 (M^++1, 3), 389 (M^+, 5), 308 (100), 306 (19), 262 (19), 227 (1), 177 (4), 145 (2), 105 (2), 91 (2), 77 (4), Anal. Calcd for $C_{21}H_{19}N_5O_3$ (389.41): C, 64.77; H, 4.92; N, 17.98. Found: C, 64.55; H, 5.20; N, 17.70 %.

4-Cyclohexyl-1-(1-naphthyl)[1,2,4]triazolo[4,3-a]quinazolin-5(4H)-one (**5f**): white yellow crystals (yield 80%), mp 120 °C (EtOH-water). IR (KBr) ν 1677 (C=O), 1611 (C=N) cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.2-3.7 (m, 10H, cyclohexyl), 5.2 (m, 1H, CH-N, cyclohexyl) 6.5 – 8.4 (m, 11 H, ArH). MS: m/z (%): 396 (M^++2, 1), 395 (M^++1, 2), 394 (M^+, 9), 339 (4), 313 (100), 311 (88), 241 (6), 227 (6), 228 (10), 145 (4), 135 (22) 127 (4), 90 (8), 77 (5). Anal. Calcd for $C_{25}H_{22}N_4O$ (394.47): C, 76.12; H, 5.62; N, 14.20. Found: C, 76.07; H, 5.72; N, 14.47 %.

1-(2-Furyl)-4-cyclohexyl[1,2,4]triazolo[4,3-a]quinazolin-5(4H)-one (**5g**): white yellow crystals (yield 83%), mp 215 °C (EtOH). IR (KBr) ν 1696 (C=O), 1604 (C=N) cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.2-2.8 (m, 10H, cyclohexyl), 5.2 (m, 1H, CH-N, cyclohexyl) 6.7 – 8.4 (m, 7 H, ArH). MS: m/z (%): 335 (M^++1, 3), 334 (M^+, 9), 255 (3), 253 (100), 251 (7), 227 (1), 198 (20), 195 (5), 169 (5), 145 (4), 130 (4), 90 (8), 77 (4). Anal. Calcd for $C_{19}H_{18}N_4O_2$ (334.37): C, 68.25; H, 5.43; N, 16.76. Found: C, 68.10; H, 5.23; N, 16.38 %.

1-(2-Thienyl)-4-cyclohexy[1,2,4]triazolo[4,3-a]quinazolin-5(4H)-one (**5h**): pale green crystals (yield 85%), mp 210 °C (EtOH). IR (KBr) ν 1679 (C=O), 1610 (C=N) cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.2-2.8 (m, 10H, cyclohexyl), 5.2 (m, 1H, CH-N, cyclohexyl) 7.2 – 8.4 (m, 7 H, ArH). MS: m/z (%): 352 (M^++2, 2) 351 (M^++1, 3), 350 (M^+, 6), 269 (100), 267 (38), 227 (4), 212 (3), 185 (7), 145 (8), 109 (7), 104 (11), 90 (15), 77 (9). Anal. Calcd for $C_{19}H_{18}N_4OS$ (350.44): C, 65.12; H, 5.18; N, 15.99. Found: C, 64.99; H, 5.02; N, 15.72 %.

2,4-Disubstituted[1,2,4]triazolo[1,5-a]quinazolin-5(4H)-ones (**6**):

General procedure - To a solution of **5** (1 mmol) in absolute EtOH (15 mL) was added potassium hydroxide (0.25 g) and the mixture was refluxed for 4 h and cooled. The solid that precipitated upon neutralization with hydrochloric acid (6 M), was filtered, washed with water, dried and finally crystallized from an appropriate solvent. The various products that were isolated are listed below together with their physical constants and spectral data.

2-Phenyl-4-cyclohexy[1,2,4]triazolo[1,5-a]quinazolin-5(4H)-one (**6a**): white solid (yield 78%), mp 228°C (EtOH). IR (KBr) ν 1701 (C=O), 1590 (C=N) cm^{-1}. ^1H NMR (DMSO-d_6): δ 1.2-1.9 (m, 10H, cyclohexyl), 5.3 (m, 1H, CH-N, cyclohexyl) 7.2 – 8.0 (m, 9 H, ArH). MS: m/z (%): 345 (M^++1, 2), 344 (M^+, 3), 343 (4), 319 (9) 280 (37), 263 (72), 261 (38), 235 (100), 227 (3), 226 (11), 224 (12), 160 (6), 145 (7), 132 (17), 105 (21), 90 (13), 77 (22). Anal. Calcd for $C_{21}H_{20}N_4O$ (344.41) : C, 73.23; H, 5.85; N, 16.27. Found: C, 73.12; H, 5.65; N, 16.36 %.

2-(4-Tolyl)-4-cyclohexyl[1,2,4]triazolo[1,5-a]quinazolin-5(4H)-one (**6b**): white crystals (yield 75%), mp 276 °C (EtOH -DMF). IR (KBr) ν 1703 (C=O), 1588 (C=N) cm^{-1}. ^1H NMR (DMSO-d_6): δ 1.1-1.9 (m, 10H, cyclohexyl), 2.2 (s, 3H, CH_3), 5.3 (m, 1H, CH-N, cyclohexyl), 7.0 – 8.0 (m, 8 H, ArH). MS: m/z (%): 359 (M^++1, 4), 358 (M^+, 5), 313 (15), 295 (6), 293 (22), 277 (100), 275 (52), 249 ((14), 177 (4), 160 (10), 133 (13), 104 (8), 90 (8), 77 (4). Anal. Calcd for $C_{22}H_{22}N_4O$ (358.44): C, 73.72; H, 6.19; N, 15.63. Found: C, 73.65; H, 6.04; N, 15.76 %.

2-(4-Chlorophenyl)-4-cyclohexyl[1,2,4]triazolo[1,5-a]quinazolin-5(4H)-one (**6c**): brown crystals (yield 82%), mp 243 °C (EtOH -DMF). IR (KBr) ν 1704 (C=O), 1585 (C=N) cm^{-1}. ^1H NMR (DMSO-d_6): δ 1.1-1.9 (m, 10H, cyclohexyl), 5.3 (m, 1H, CH-N, cyclohexyl) 7.2 – 8.0 (m, 8 H, ArH). MS: m/z (%): 379 (M^++1, 2) 378 (M^+, 3), 353 (12), 341 (7) 317 (8), 314 (49) 299 (32), 297 (100), 271 (28), 269 (89), 260 (14), 227 (4), 184 (5), 145 (8), 139 (11), 90 (8), 77 (8). Anal. Calcd for $C_{21}H_{19}ClN_4O$ (378.85): C, 66.58; H, 5.05; N, 14.79. Found: C, 66.41; H, 5.08; N, 14.68 %.

2-(4-Methoxyphenyl)-4-cyclohexyl[1,2,4]triazolo[1,5-a]quinazolin-5(4H)-one (**6d**): white crystals (yield 77%), mp 215 °C (EtOH -DMF). IR (KBr) ν 1671 (C=O), 1608 (C=N) cm^{-1}. ^1H NMR (DMSO-d_6): δ 1.1-1.9 (m, 10H, cyclohexyl), 3.7 (s, 3H, CH_3), 5.3 (m, 1H, CH-N, cyclohexyl), 6.8 – 8.0 (m, 8 H, ArH). MS: m/z (%): 375 (M^++1, 4), 374 (M^+, 6), 319 (4), 293 (100), 248 (10), 227 (3), 160 (4), 145 (8), 103 (5), 90 (9), 77 (3). Anal. Calcd for $C_{22}H_{22}N_4O_2$ (374.44): C, 70.57; H, 5.92; N, 14.96. Found: C, 70.40; H, 5.73; N, 14.82 %.

2-(4-Nitrophenyl)-4-cyclohexyl[1,2,4]triazolo[1,5-a]quinazolin-5(4H)-one (**6e**): yellow brown crystals (yield 78%), mp 202 ^{o}C (EtOH -water). IR (KBr) ν 1659 (C=O), 1567 (C=N) cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 1.1-1.9 (m, 10H, cyclohexyl), 5.3 (m, 1H, CH-N, cyclohexyl) 7.3 – 8.1 (m, 8 H, ArH). MS: m/z (%):391 (M^++2, 3), 390 (M^++1, 3), 389 (M^+, 5), 311 (100), 308 (100), 277 (91), 118 (55), 105 (18), 91 (27), 82 (25), 76 (41),. Anal. Calcd for $C_{21}H_{19}N_5O_3$ (389.41): C, 64.77; H, 4.92; N, 17.98. Found: C, 64.50; H, 4.61; N, 17.70 %.

2-(1-Naphthyl)-4-cyclohexyl[1,2,4]triazolo[1,5-a]quinazolin-5(4H)-one (**6f**): white crystals (yield 75%), mp 228 ^{o}C (EtOH-DMF). IR (KBr) ν 1668 (C=O), 1566 (C=N) cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 1.0-2.0 (m, 10H, cyclohexyl), 5.3 (m, 1H, CH-N, cyclohexyl) 7.3 – 8.2 (m, 11 H, ArH). MS: m/z (%): 395 (M^++1, 6), 394 (M^+, 9), 357 (6), 313 (100), 277 (81), 275 (41), 242 (4), 227 (6), 160 (6) 153 (13), 144 (3), 132 (9) 118 (5), 90 (5), 77 (3). Anal. Calcd for $C_{25}H_{22}N_4O$ (394.47): C, 76.12; H, 5.62; N, 14.20. Found: C, 76.05; H, 5.76; N, 13.88 %.

2-(2-Furyl)-4-cyclohexyl[1,2,4]triazolo[1,5-a]quinazolin-5(4H)-one (**6g**): white crystals (yield 75%), mp 235 ^{o}C (EtOH -DMF). IR (KBr) ν 1704 (C=O), 1593 (C=N) cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 1.0-1.9 (m, 10H, cyclohexyl), 5.3 (m, 1H, CH-N, cyclohexyl), 5.7 – 8.1 (m, 7H, ArH). MS: m/z (%): 334 (M^+, 2), 309 (9), 253 (18), 227 (3), 225 (100), 216 (17), 172 (37), 145 (11), 146 (23), 105 (6), 90 (10), 77 (11). Anal. Calcd for $C_{19}H_{18}N_4O_2$ (334.37): C, 68.25; H, 5.43; N, 16.76. Found: C, 68.18; H, 5.27; N, 16.38 %.

2-(2-Thienyl)-4-cyclohexyl[1,2,4]triazolo[1,5-a]quinazolin-5(4H)-one (**6h**): white crystals (yield 76%), mp 246 ^{o}C (EtOH -DMF). IR (KBr) ν 1703 (C=O), 1590 (C=N) cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 1.0-1.9 (m, 10H, cyclohexyl), 5.3 (m, 1H, CH-N, cyclohexyl), 6.3 – 8.1 (m, 7H, ArH). MS: m/z (%): 351 (M^++1, 3), 350 (M^+, 5), 325 (5), 286 (23), 269 (100), 241 (32), 227 (3), 185 (8), 145 (6), 132 (5), 90 (7), 77 (5). Anal. Calcd for $C_{19}H_{18}N_4OS$ (350.44): C, 65.12; H, 5.18; N, 15.99. Found: C, 65.05; H, 5.09; N, 15.70 %.

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