A new strategy for the synthesis of novel spiro[indoline-3,2'-thiazolo[5,4-*e*]pyrimido[1,2-*a*]pyrimidine] derivatives

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Abstract

An environmentally benign, efficient and facile route is developed for the synthesis of novel spiro[indoline-3,2'-thiazolo[5,4-*e*]pyrimido[1,2-*a*]pyrimidine] derivatives. The benzylidene derivatives of spiro[indoline-thiazolidinones] **6** containing an α,β-unsaturated ketonic function [-CH=CH-CO-] have been used as a component of Michael addition with an equimolar amount of 2-aminopyrimidine **7** to give a series of novel spiroindole derivatives **9** in a single step using montmorillonite KSF as inorganic solid support with few drops of DMF. In comparison to conventional synthesis involving tedious multistep procedures, the present method indicates operational simplicity, shorter reaction time and higher yields which can prove this procedure as a useful alternative for the synthesis of novel spiro heterocycles.

Keywords: Spiro[indoline-thiazolidinone], spiro[indoline-thiazolo-pyrimidopyrimidine], montmorillonite KSF, DMF

Introduction

Heterocyclic scaffolds represent the central framework of many biologically active compounds. Among the various heterocyclic systems, indole holds a prominent place because it is present as a core unit in a number of compounds possessing a broad spectrum of biological activities.[1-2] It is well known that the heterocyclic spiro-oxindole framework is an important structural motif in biologically relevant compounds as natural products and pharmaceuticals,[3] e.g., surugatoxin, horsfiline, spirotryprostatin A&B, elacomine, gelsemine, alstonisine and strychnofoline.

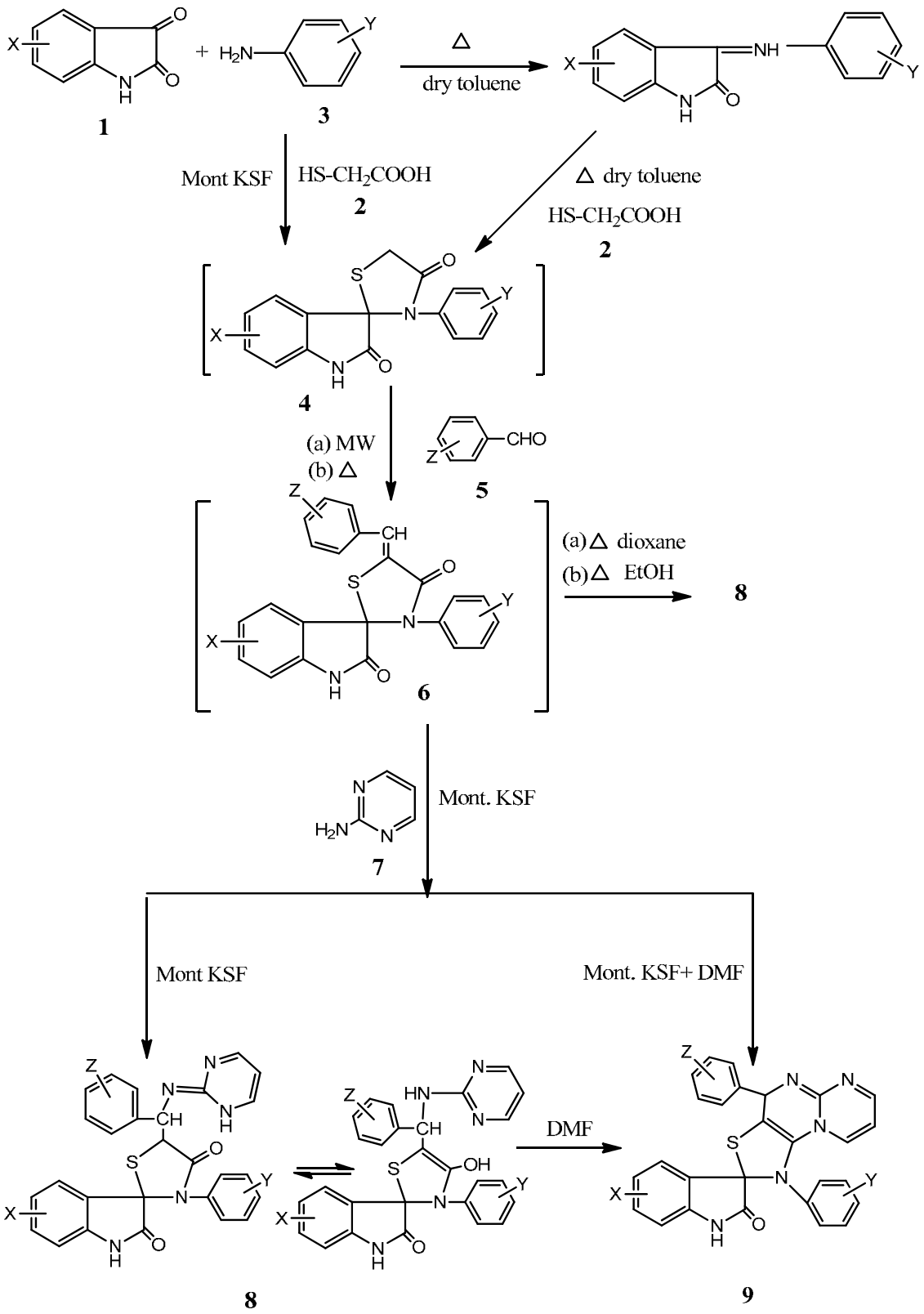
Further, the chemistry of spiro-indoles in which an indole ring is joined to sulfur and nitrogen containing heterocycles at the C-3 position through a spiro carbon atom is of great interest due to their physiological and biological activities.[4-5] Spiro[indole-thiazolidinones] are known to possess various biological activities including antiinflammatory,[6] antimicrobial,[7] bacteriostatic,[8] anticonvulsant[9] and used as antifungal agents.[10] In addition, the synthesis of pyridopyrimidine

and their derivatives is of high interest in organic chemistry due to their potential biological and pharmacological activities such as antiviral,[11-12] antiinflammatory,[13] insecticidal,[14] antifolate,[15] tyrosine kinase inhibitor,[16] antimicrobial,[17] calcium channel antagonists,[18] antileishmanial,[19] diuretic and potassium-sparing.[20] On the other hand thiazolo-pyrimidines are important class of compounds with wide range of biological activity.[21] It has been observed that the incorporation of more than one bioactive heterocyclic moiety into a single framework may result into the production of novel heterocycles with enhanced bioactivity.[22] Further, annulation of heterocyclic ring often improves biological properties such as potency, selectivity, toxicity and metabolic stability.[23]

Keeping in view of diverse biological activities associated with spiroindoles, pyrimidopyrimidines and thiazolopyrimidines, it was thought to construct a novel system which may combine these bioactive rings together in a single molecular framework to see the additive effects towards their biological activities. Further, a literature survey reveals no report on the synthesis of title novel nucleus yet so far. As part of our ongoing program to develop efficient and robust methods for the preparation of biologically relevant compounds[24] from readily available building blocks, which are novel yet resemble known biologically active molecules by virtue of the presence of some critical structural features, we have developed a facile, efficient, one-pot method for the synthesis of novel spiro[indoline-3,2'-thiazolo[5,4-*e*]pyrimido[1,2-*a*]pyrimidin]-2(1*H*)-one **9a-d** by the reaction of 5'-benzylidene-3'-phenylspiro[indoline-3,2'-thiazolidine]-2,4'(1*H*)-dione **6a-d** with 2-aminopyrimidine **7** using montmorillonite KSF with few drops of DMF under microwave irradiation (scheme-1) and its comparison with synthesis under conventional conditions, which involves multistep tedious procedure requiring excessive use of solvent and extra labor for separation and purification of compounds as various steps.

Results and Discussion

The required biologically important scaffold spiro[indoline-thiazolidinones] **4** were prepared by the improved solvent free multicomponent condensation between substituted indole-2,3-diones **1**, thioglycolic acid **2** and amines **3** using montmorillonite KSF as solid support. The required compound **4** was formed in reasonable purity (TLC) and could be used as such for next step without further purification. The reaction of **4** with benzaldehyde **5** yielded 5'-benzylidene-3'-phenylspiro[indoline-3,2'-thiazolidine]-2,4'(1*H*)-dione **6** *"in situ"* in 4-5 min under same reaction conditions in one-pot. The spiro[indoline-thiazolidinones] system has been synthesized earlier conventionally by a two step procedure in 40–60% yield using isatin-3-imines as key intermediate, which were synthesized from substituted isatins and aromatic amines. The classical methods involving either the azeotropic removal of water[25] or reaction in presence of dehydrating agent[26] and use of large amount of volatile and toxic solvents at elevated temperature for several hours of heating were of some utility. Further, the products are generally purified by crystallization or column chromatography with further need of solvent.


dry toluene
Mont KSF
HS-CH2COOH
2
dry toluene
HS-CH2COOH
2
(a) MW
(b) △
5
(a)△ dioxane
(b)△ EtOH
8
Mont. KSF
Mont KSF
Mont. KSF+ DMF
DMF
1
3
4
6
7
8
9

Scheme 1

The benzylidene derivatives **6** containing an α,β unsaturated ketonic functional group in their structure have been used as a component of Michael addition with 2-aminopyrimidine to afford novel spiro compound using montmorillonite KSF. However, the results obtained from spectral studies showed the formation of uncyclized Michael adduct **8a** instead of expected spiro derivative **9** even after irradiating the reaction mixture for long duration of time (30 minutes). The desired spiro compound **9** was formed successfully within 4-5 minutes by adding few drops of DMF in the same reaction mixture (scheme-1). The reaction times and product yields for various substrates are summarized in Table 1. The ability of DMF is to act as energy transfer agent and homogenizer to increase the reaction temperature was also advocated by Loupy and co-workers.[27] It did not lead to any side reaction and no detectable by-products were observed. Hence, the results showed that the combination of clay with DMF is most suitable reaction medium for present investigation involving the annulation of pyrimidine ring on 5'-benzylidene-3'-phenylspiro[indoline-3,2'-thiazolidine]-2,4'(1*H*)-dione **6** in single step. Further, to check the possibility of formation of **8** or **9**, the reaction of **6a** with 2-aminopyrimidine was also carried out conventionally using fused sodium acetate in dioxane and in ethanol containing 4-5 drops of glacial acetic acid. The results showed the formation of Michael adduct 3'-(4-chlorophenyl)-5'-[(4-(dimethylamino)phenyl)(pyrimidin-2(1*H*)-ylideneamino)methyl]spiro[indoline-3,2'-thiazolidine]-2,4'-dione **8a** instead of required spiro product in both cases.

Table 1. Synthesis of 5'-benzylidene-3'-phenylspiro[indoline-3,2'-thiazolidine]-2,4'(1*H*)-diones **6a-d** and spiro[indoline-3,2'-thiazolo[5,4-*e*]pyrimido[1,2-*a*]pyrimidin]-2(1*H*)-one **9a-d** derivatives

Products	X	Y	Z	Time (min)	Yield (%)[a]	mp (°C)
6a	H	4-Cl	4-$N(CH_3)_2$	6-8	88	243-245
6b	5-Br	4-CH_3	4-OCH_3	6-8	92	254-256
6c	5-CH_3	4-Cl	4-$N(CH_3)_2$	6-8	89	136-138
6d	H	4-F	4-$N(CH_3)_2$	6-8	87	183-185
9a	H	4-Cl	4-$N(CH_3)_2$	7-8	88	140-145
9b	5-Br	4-CH_3	4-OCH_3	7-8	89	213-215
9c	5-CH_3	4-Cl	4-$N(CH_3)_2$	7-8	83	203-205
9d	H	4-F	4-$N(CH_3)_2$	7-8	84	279-281

[a] Yields refer to the isolated pure products.

Conclusions

From the above studies we can advocate this method as facile, efficient and environ-economic for the one-pot synthesis of a series of spiro[indoline-3,2'-thiazolo[5,4-*e*]pyrimido[1,2-*a*]pyrimidin]-2(1*H*)-one **9a-d** with few drops of DMF using montmorillonite KSF as inorganic solid support.

Experimental Section

General. Reagents and solvents were obtained from commercial sources and used without further purification. Melting points were determined on a Toshniwal apparatus. The elemental and spectral analyses of synthesized compounds have been carried out at the Central Drug Research Institute, Lucknow and Regional Sophisticated Instrumentation Centre, Chandigarh. The purity of compounds was checked on thin layers of silica gel in various non-aqueous solvent systems, for e.g. benzene: ethylacetate (9:1), benzene: dichloromethane (8:2). IR spectra (KBr) were recorded on a Magna FT IR–550 spectrophotometer and ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker DRX-300 using $CDCl_3$ at 300.15 and 75.46 respectively. TMS was used as internal reference. Mass spectrum of representative compound was recorded on Kratos 50 mass spectrometer at 70 eV. The microwave-assisted reactions were carried out in a commercial multimode MW oven equipped with inverter technology and also attached with a magnetic stirrer and reflux condenser, operating at 1000W generating 2450 MHz frequency.

Synthesis of 3'-phenylspiro[indoline-3,2'-thiazolidine]-2,4'(1*H*)-diones 4. These compounds were synthesized in one-pot by multicomponent cyclocondensation reaction of indole-2,3-dione, amines and thioglycolic acid using montmorillonite KSF as solid support as previously reported by us.[28] Since TLC studies showed 100% conversion with formation of single product hence it is used as such for further conversion without isolating them. For structural confirmations, some products are isolated by desorption with methanol and compared with authentic samples prepared by literature methods.[29]

Synthesis of 3'-(4-chlorophenyl)-5'-[4-(dimethylamino)benzylidene]spiro[indoline-3,2'-thiazolidine]-2,4'(1*H*)-dione 6a. It was synthesized by following methods

1. Conventional method. [30] An equimolar mixture of 3'-(4-chlorophenyl)spiro[indoline-3,2'-thiazolidine]-2,4'(1*H*)-dione **4a** (0.01 mol), 4-(dimethylamino)benzaldehyde **5a** (0.01 mol) and anhydrous sodium acetate in glacial acetic acid (10 ml) was refluxed for 4-5 h. On cooling, the reaction mixture was poured into ice-cold water. The solid thus obtained was filtered, washed with water, dried and crystallized from ethyl acetate. The obtained yield was 52%

2. Nonconventional method. An equimolar mixture of 4-(dimethylamino)benzaldehyde **5a** (0.01mol) and 3'-(4-chlorophenyl)spiro[indoline-3,2'-thiazolidine]-2,4'(1*H*)-dione **4a** (synthesized *in situ*) were adsorbed on montmorillonite KSF (2g) with methanol, mixed

thoroughly and irradiated for an appropriate time until the completion of the reaction (monitored by TLC). The recyclable solid support was separated by filtration after eluting the product with methanol and excess solvent was evaporated on a rotary evaporator to give solid, which was recrystallized from methanol to give desired product.

6a. Mp 243-245°C; IR (KBr, cm^{-1}) ν_{max} 3250-3280 (NH), 1733, 1690 (both C=O) and 1630 (C=C); ^1H NMR (300 MHz, $CDCl_3$) δ_H: 2.44 (s, 6H, $N(CH_3)_2$), 5.10 (s , 1H, CH), 7.13-7.64 (m, 12H, Ar-H), 9.23 (s, 1H, NH exchanges with D_2O); ^{13}C NMR (74.46 MHz, $CDCl_3$) δ_C: 81.6 (spiro carbon), 112.3-143.3 (olefinic carbon and aromatic carbons), 162.8, 168.2 (both C=O); Anal. calcd for $C_{25}H_{20}ClN_3O_2S$: C, 65.00; H, 4.36; N, 9.10. Found: C, 65.20; H, 4.35; N, 9.13

5-Bromo-5'-(4-methoxybenzylidene)-3'-*p*-tolylspiro[indoline-3,2'-thiazolidine]-2,4'(1*H*)-dione 6b. Mp 254-256°C; IR (KBr, cm^{-1}) ν_{max} 3370-3250 (NH), 1715, 1690 (both C=O), 1630 (C=C); ^1H NMR (300 MHz, $CDCl_3$) δ_H: 1.43 (s, 3H, CH_3), 3.62 (s, 3H, OCH_3), 5.21 (s, 1H, CH), 7.05-7.68 (m, 11H. Ar-H), 9.28 (s, 1H, NH exchanges with D_2O). Anal. calcd for $C_{25}H_{19}BrN_2O_3S$: C, 59.18; H, 3.77; N, 5.52. Found: C, 58.90; H, 3.76; N, 5.49

3'-(4-Chlorophenyl)-5'-[4-(dimethylamino)benzylidene]-5-methylspiro[indoline-3,2'-thiazolidine]-2,4'(1*H*)-dione 6c. Mp 136-138°C; IR (KBr, cm^{-1}) ν_{max} 3360-3290 (NH), 1720, 1695 (both C=O), 1628 (C=C); ^1H NMR (300 MHz, $CDCl_3$) δ_H: 1.9 (s, 3H, CH_3), 2.24 (s, 6H, $N(CH_3)_2$), 5.4 (s, 1H, CH), 7.10-7.85 (m, 11H, Ar-H). 9.36 (s, 1H, NH exchanges with D_2O). Anal. calcd for $C_{26}H_{22}ClN_3O_2S$: C, 65.61; H, 4.66; N, 8.83. Found: C, 65.42; H, 4.65; N, 8.87

5'-[4-(Dimethylamino)benzylidene]-3'-(4-fluorophenyl)spiro[indoline-3,2'-thiazolidine]-2,4'(1*H*)-dione 6d. Mp 183-185°C; IR (KBr, cm^{-1}) ν_{max} 3390-3280 (NH), 1710, 1690 (both C=O), 1630 (C=C); ^1H NMR (300 MHz, $CDCl_3$) δ_H: 2.28 (s, 6H, $N(CH_3)_2$), 5.18 (s, 1H, CH), 7.15-7.89 (m, 12H. Ar-H), 9.23 (s, 1H, NH exchanges with D_2O). Anal. calcd for $C_{25}H_{20}FN_3O_2S$: C, 67.40; H, 4.52; N, 9.43. Found: C, 67.62; H4.53; N, 9.40

Synthesis of 3'-(4-chlorophenyl)-5'-[(4-(dimethylamino)phenyl)(pyrimidin-2(1*H*) ylideneamino) methyl]spiro[indoline-3,2'-thiazolidine]-2,4'(1*H*)-dione 8a. This was synthesized by following methods.

1. Conventional methods. (i) An equimolar mixture of 3'-(4-chlorophenyl)-5'-[4-(dimethylamino)benzylidene]spiro[indoline-3,2'-thiazolidine]-2,4'(1*H*)-dione **6a** (0.0l mol, 4.27 g), 2-aminopyrimidine **7** (0.01 mol, 0.94 g) and fused anhydrous sodium acetate (2 g) in dioxane (40 ml) was refluxed for 8 hrs. The solvent was removed by distillation in vacuum and residue was poured into cold water. The solid thus obtained was washed with water and crystallized from ethanol to give **8a**. Yield = 60%. (ii) An equimolar mixture of **6a** and **7** in ethanol (30 ml) containing 6-8 drops of glacial acetic acid was refluxed for 7 hrs. A crude product appeared on cooling the reaction mixture, which was filtered, washed with water and recrystallized from ethanol to give **8a**. Yield = 54%

2. Nonconventional method. An equimolar mixture (0.0l mol) of **6a** (synthesized ‘‘*in situ*’’) and 2-aminopyrimidine **7** was adsorbed on montmorillonite KSF (2gm) and the reaction mixture was irradiated for 7 min. The recyclable montmorillonite KSF was separated by eluting the product

with methanol and excess solvent was evaporated on rota-evaporator to give pure product (TLC), with no need of further purification.

Yield 92%: Mp 163-167°C; IR (KBr, cm^{-1}) ν_{max} 3352-3460 (NH), 1690, 1720 (both C=O), 1619 (C=N); ^1H NMR (300 MHz, $CDCl_3$) δ_H: 2.44 (s, 6H, $N(CH_3)_2$), 3.95-4.42 (dd, 2H, S-CH and N-CH), 6.39-7.50 (m, 15H, Ar-H), 8.83-8.84 (s, 2H, NH exchanges with D_2O). Anal. calcd for $C_{29}H_{27}ClN_6O_2S$: C, 62.30; H, 4.87; N, 15.03; Found: C, 62.05; H, 4.86; N, 15.08

Synthesis of 3'-(4-chlorophenyl)-10'-[4-(dimethylamino)phenyl]spiro[indoline-3,2'- thiazolo[5,4-*e*]pyrimido[1,2-*a*]pyrimidin]-2(1*H*)-one 9a. An equimolar mixture (0.0l mol) of **6a** and **7** was adsorbed on montmorillonite KSF (2 g) and 4-5 drops of DMF were added in reaction mixture and irradiated for 7-8 min. The recyclable montmorillonite KSF was separated by eluting the product with methanol and excess solvent was evaporated on rota-evaporator to give pure product (TLC), with no need of further purification.

Alternatively the compound **9a** was also synthesized from **8a** using few drop of DMF and irradiating under microwave until completion of the reaction (monitored by TLC). The resultant residue was crystallized from ethanol.

9a. Mp 140-145°C; IR (KBr, cm^{-1}) ν_{max} 3264-3248 (NH), 1710 (C=O), 1677(C=N); ^1H NMR (300 MHz, $CDCl_3$) δ_H: 2.58 (s, 6H, $N(CH_3)_2$), 6.61-7.62 (m, 16H, Ar-H, and CH), 10.22 (s, 1H, NH exchanges with D_2O); ^{13}C NMR (74.46 MHz, $CDCl_3$) δ_C: 32.87 (CH_3), 70.20 (spiro carbon), 111.03-140.42 (aromatic carbon), 172.63 (C=N) and 176.67 (NH-C=O). Mass spectrum m/z at 538 [M^+] (100%). Anal. calcd for $C_{29}H_{23}ClN_6OS$: C, 64.62; H, 4.30; N, 15.90; Found: C, 64.82; H, 4.31;N, 15.86.

5-Bromo-10'-(4-methoxyphenyl)-3'-*p*-tolylspiro[indoline-3,2'-thiazolo[5,4-*e*] pyrimido[1,2-*a*]pyrimidin]-2(1*H*)-one 9b. Mp 213-215°C; IR (KBr, cm^{-1}) ν_{max} 3360-3290 (NH), 1720 (C=O), 1670 (C=N); ^1H NMR (300 MHz, $CDCl_3$) δ_H: 2.36 (s, 3H, CH_3), 3.62 (s, 3H, OCH_3), 6.68-7.72 (m, 15H, Ar-H and CH), 10.15 (s, 1H, NH exchanges with D_2O). $C_{29}H_{22}BrN_5O_2S$: calc. C, 59.59; H, 3.79; N, 11.98.Found: C, 59.78; H, 3.80; N, 11.95.

3'-(4-hlorophenyl)-10'-[4-(dimethylamino)phenyl]-5-methylspiro[indoline-3,2'-thiazolo[5,4-*e*]pyrimido[1,2-*a*]pyrimidin]-2(1*H*)-one 9c. Mp 203-205°C; IR (KBr, cm^{-1}) ν_{max} 3375-3290 (NH), 1715 (C=O), 1660 (C=N); ^1H NMR (300 MHz, $CDCl_3$) δ_H: 2.36 (s, 3H, CH_3), 2.26 (s, 6H, $N(CH_3)_2$), 7.15-8.12 (m, 15H, Ar-H and CH), 10.28 (s, 1H, NH exchanges with D_2O). Anal. calcd for $C_{30}H_{25}ClN_6OS$: C, 65.15; H, 4.56; N, 15.20. Found: C, 64.94; H, 4.57; N, 15.25.

10'-[4-(Dimethylamino)phenyl]-3'-(4-fluorophenyl)-spiro[indoline-3,2'-thiazolo[5,4-*e*]pyrimido [1,2-*a*]pyrimidin]-2(1*H*)-one 9d. Mp 279-281°C; IR (KBr, cm^{-1}) ν_{max} 3360-3250 (NH), 1710 (C=O), 1648 (C=N); ^1H NMR (300 MHz, $CDCl_3$) δ_H: 2.58 (s, 6H, $N(CH_3)_2$), 7.10-8.02 (m, 16H, Ar-H and CH), 10.16 (s, 1H, NH exchanges with D_2O). Anal. calcd for $C_{29}H_{23}FN_6OS$: C, 66.65; H, 4.44; N, 16.08. Found: C, 66.35; H, 4.45; N, 16.04.

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