Regioselective Synthesis of Novel Spiroheterocyclic Framework via the 1,3-Dipolar Cycloaddition

Xiaofen Hu [a], Yaqing Feng* [a], Weiyi Zhou [b], Kangjian Qiao [a]

[a] Department of Fine Chemicals, School of Chemical Engineering and Technology, Tianjin University, Tianjin, 300072, P.R. China
[b] Analysis Center, Tianjin University, Tianjin, 300072, P.R. China

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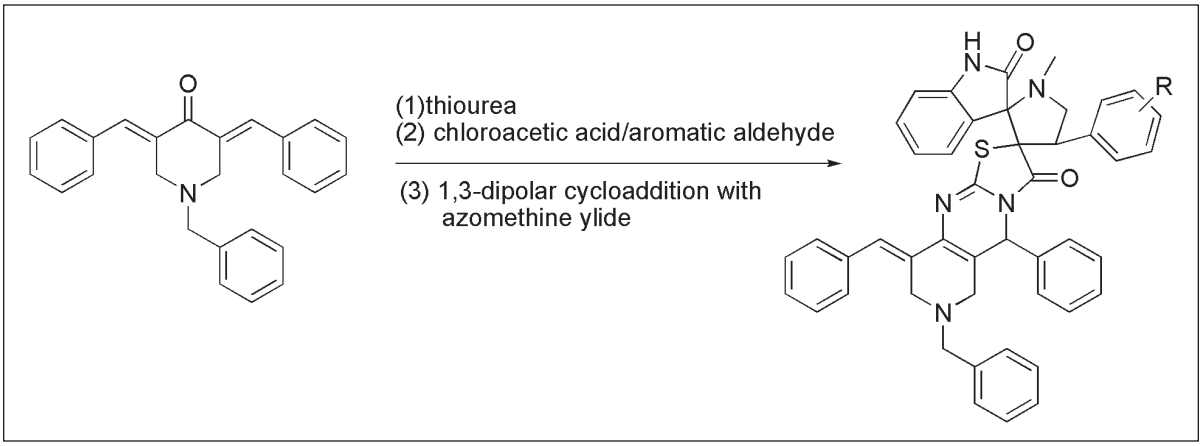

A series of novel dispiro[oxindole-fused pyrimidine]pyrrolidine ring systems **4a-f** were synthesized by the regioselective 1,3-dipolar cycloaddition reaction of the 2-arylmethylene-7-benzyl-9-(benzylidene)tetrahydropyrido[4,3-*d*]thiazolo[3,2-*a*]pyrimidin-3-ones **1a-f** with azomethine ylides, generating by the decarboxylative route from isatin **2** and sarcosine **3**, in moderate to good yields. The regiochemistry of designed dispiroheterocyclic compounds **4a-f** was established by single crystal X-ray structure and spectroscopic techniques.

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Introdution.

Intermolecular 1,3-dipolar cycloaddition reaction of azomethine ylides with exocyclic double bonds represents an efficient and convergent method for the construction of the spiropyrrolidine structural unit widely occurring in natural substances characterized by highly pronounced biological properties [1-3]. Systematic investigation of spiroindoles has also drawn much attention due to the fact that if the indole ring is joined to the other heterocyclic systems through a spiro carbon atom at C-3, the resulting compounds show an increased spectrum of biological activities [4-6]. Moreover, varied pharmacological properties are associated with the fused pyrimidine ring system containing substituted six-membered ring [7-8]. Thus it is expected that production of a dispiro[oxindole-fused pyrimidine]pyrrolidine ring system would enhance the biological activity significantly.

As a part of our endeavor to explore the synthetic potentiality in the construction of novel spiro pyrrolidine derivates and also to study their biological applications [9-10], we herein report the regioselective cycloaddition of various heterocyclic compounds **1a-f** with the ylide generated from isatin **2** and sarcosine **3** by a decarboxylative route [11].

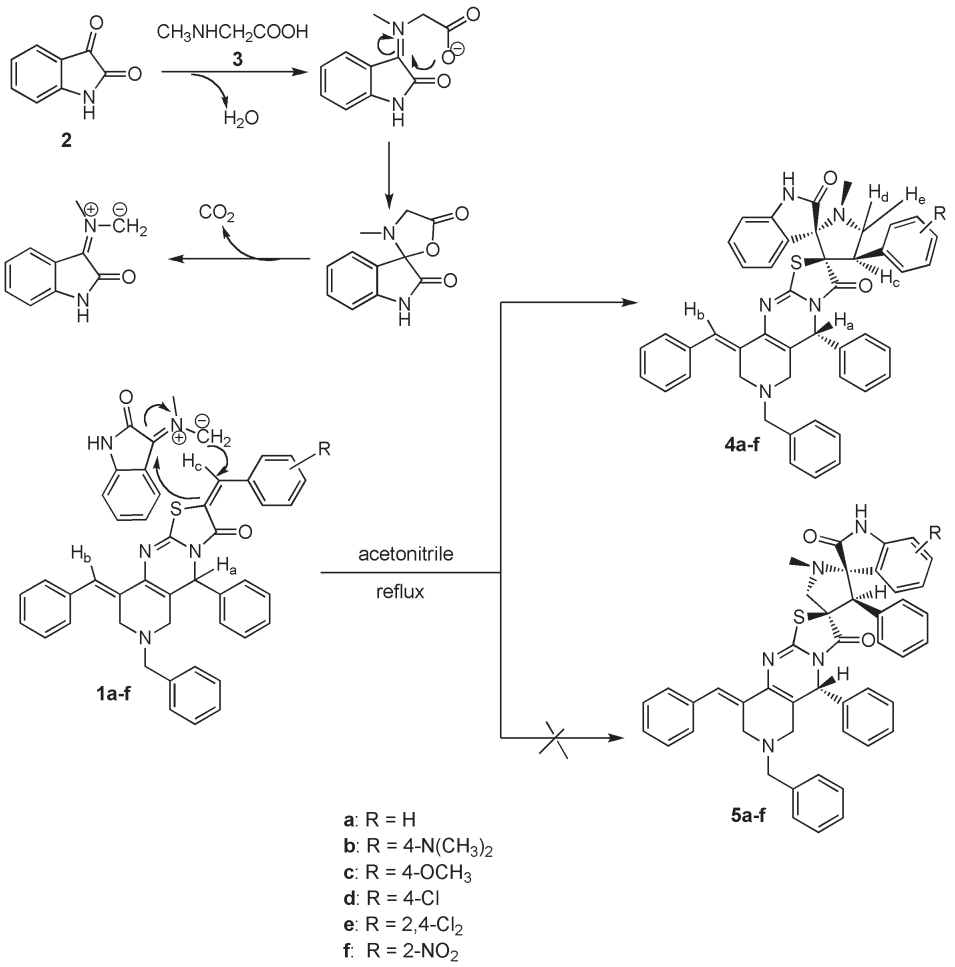
Results and Discussion.

The reaction of isatin **2** with sarcosine **3** in boiling acetonitrile leads to the formation of an azomethine ylide which readily undergoes 1,3-dipolar cycloaddition reactions with compounds **1a-f** to give a single cycloadduct, in a one pot three component process, as evidenced by TLC and mass spectral studies. The reaction afforded a series of novel dispiroheterocycles **4a-f** containing the oxindole ring system by a regioselective cycloaddition of the azomethine ylide to the exocyclic double bond of thiazolinone ring system in all case. No trace of the other regioisomers

5a-f were detected, due to steric effect between the oxindole ring and aryl group of the 2- arylmethylene (Scheme 1).

The structure of each product **4a-f** and the regiochemistry of cycloaddition have been confirmed by spectroscopic data. For example the IR spectrum of **4a** showed two carbonyl peaks at 1700 and 1721 cm^{-1} which corresponds to the oxindole and thiazolinone ring carbonyls, respectively. It also exhibited a peak at 1363 cm^{-1} due to the $-CH_3$ of the pyrrolidine and at 3421 cm^{-1} due to the -NH of the oxindole. The ^1H NMR spectrum of **4a** exhibited several characteristic peaks at δ values 2.21 (s, 3H,

Scheme 1



-CH_3), 2.73 (d, J = 17.0 Hz, 1H, Pyridine-H), 3.05 (d, J = 17.0 Hz, 1H, Pyridine-H), 3.33 (d, J = 14.0 Hz, 1H, Pyridine-H), 3.35 (d, J = 12.5 Hz, 1H, Benzyl-H), 3.42-3.45 (m, 1H, H_d), 3.46 (d, J = 12.5 Hz, 1H, Benzyl-H), 3.74 (d, J = 14.0 Hz, 1H, Pyridine-H), 4.03-4.07 (m, 1H, H_e), 4.13-4.17 (m, 1H, H_c), 5.52 (s, 1H, H_a), 7.89 (bs, 1H, -NH), and peaks at δ values 6.82-7.46 due to aromatic protons and H_b proton. The ^{13}C NMR spectra of **4a** exhibited the presence of benzylic carbons at δ 55.01, 58.60 and 61.10, spiro carbons at δ 70.68 and 79.84, *N*-methyl carbon at δ 35.42, N-CH_2 at δ 57.85, carbonyl carbons at δ 174.54 and 177.13. These observed chemical shift values confirmed the proposed structure. The mass spectrum of **4a** showed a peak at *m/z* 725 (M^+).

Finally, X-ray analysis (Figure 1**,** Table 1) confirmed the structure of **4a** with the proposed regiochemistry. Bond lengths and angles (Table 2 and Table 3) do not show surprising features. The pyrrolidine ring moiety is not planar, with an envelope conformation, atom N4 lies 0.554(3) Å above the C1, C10-C12 plane in the pyrrolidine ring, forming the flap of the envelope. The dihedral angle between the C12, N5, C11 and C1, C10-C12 planes is 39.8(2)°. The phenyl group (C40-C45) is rotated at angle of 74.9(2)° with respect to the C1, C10-C12 plane, due to steric hindrance. The 2-oxoindole system (C12-C19, N5) is nearly planar, makes a dihedral angle of 79.7(2)° with the C1, C10-C12 plane. The five-membered thiazolidone ring (C1-C3, S1, N1), fused to the pyrimidine ring, is nearly planar and makes a dihedral angle of 96.4(2)° with the adjacent C1, C10-C12 plane. Atoms N1-N2, C3-C5 of the six-membered dihydropyrimidine ring are almost coplanar, due to electron delocalization. Atom C6 lies 0.381(3) Å above this plane. The phenyl group (C20-C25) is rotated at angle of 91.5(2)° with respect to the N1-N2, C3-C5 plane. Atoms C4-C9 of the tetrahydropyridine ring are almost coplanar, atom N3 lies 0.580(3) Å above this plane. And the C4-C9 plane makes dihedral angles of 111.7(2)° and 26.9(2)°, respectively, with the phenyl ring C27-C32 and C34-C39.

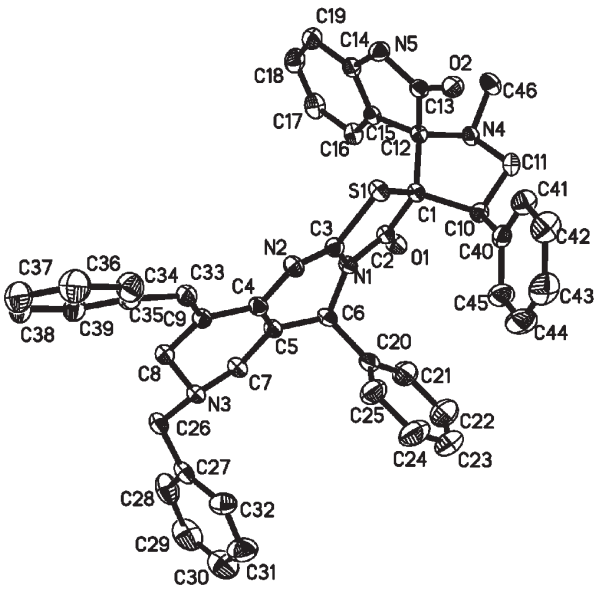


Figure 1. Single crystal X-ray diffraction of **4a** with atom numbering, showing 30% probability ellipsoids for the non-hydrogen atoms. Hydrogen atoms are omitted for clarity.

azomethine ylide generated from isatin **2** and sarcosine **3**.

EXPERIMENTAL

IR spectra were recorded on a Nicolret 5-DX FT-IR instrument. Mass spectra were recorded on a Finnigan LCQ spectrometer. ^{1}H and ^{13}C NMR spectra were recorded in deuteriochloroform using tetramethylsilane as an internal standard on an INOVA spectrometer at 500 and 125 MHz, respectively. Elemental analyses were carried out on a Fose Heraeus instrument. X-ray data was recorded using SMART-1000 CCD automatic diffractometer. Column chromatography was performed on silica gel (100-200 mesh). The raw materials **1a-f** were prepared according to the method previously described by the authors [7,12].

Crystal Structure Determinations.

Compound **4a** (20 mg) was dissolved in 15 ml of acetonitrile. The solution was kept at room temperature for 20 days to give colorless single crystals of **4a**, suitable for X-ray analysis. Molecular formula: $C_{46}H_{39}N_5O_2S$. Molecular weight 725.88, triclinic, space group P-1, a = 12.0628(18) Å, b = 12.7719(18) Å, c = 14.662(2) Å, D_c = 1.256 mg/m^3, V = 1919.6(5) Å^3, α = 73.748(2), β = 74.358(2), γ = 63.930(2). MoKa radiation, λ = 0.71073 Å, absorption coefficient = 0.130 mm^{-1}, F(000) = 764. The crystal is pale yellow and slap shaped. Number of atoms = 93. A crystal with dimensions of 0.24x0.20x0.14 mm^3 was used for X-ray data collection at 294(2) K. θ Range for data collection

Table 1
Atomic Coordinates (x10^4) and Equivalent Isotropic Displacement Parameters (Å^2 x 10^3) for Compound **4a**

atom	x	y	z	U (eq)	atom	x	y	z	U (eq)
S(1)	6933(1)	1046(1)	2696(1)	37(1)	C(20)	9129(2)	3187(2)	606(2)	45(1)
N(1)	7302(2)	2935(1)	1738(1)	32(1)	C(21)	9828(3)	3562(3)	947(2)	69(1)
N(2)	6710(2)	2017(1)	859(1)	37(1)	C(22)	11127(3)	3067(4)	721(3)	99(1)
N(3)	6805(2)	4692(2)	-1587(1)	37(1)	C(23)	11714(3)	2228(4)	152(3)	104(1)
N(4)	7256(2)	1919(1)	4964(1)	35(1)	C(24)	11033(3)	1843(4)	-179(3)	99(1)
N(5)	4679(2)	1517(2)	4887(1)	41(1)	C(25)	9736(2)	2332(3)	45(2)	70(1)
O(1)	7570(1)	3696(1)	2849(1)	44(1)	C(26)	6537(2)	5804(2)	-2288(2)	48(1)
O(2)	6589(1)	-50(1)	4765(1)	44(1)	C(27)	7650(2)	6146(2)	-2687(2)	49(1)
C(1)	7362(2)	1799(2)	3352(1)	30(1)	C(28)	7486(3)	7321(3)	-3001(2)	78(1)
C(2)	7392(2)	2930(2)	2653(1)	33(1)	C(29)	8527(4)	7619(3)	-3449(2)	95(1)
C(3)	6987(2)	2066(2)	1621(1)	33(1)	C(30)	9690(4)	6760(4)	-3577(2)	94(1)
C(4)	6637(2)	3009(2)	90(1)	35(1)	C(31)	9867(3)	5608(3)	-3252(2)	82(1)
C(5)	7060(2)	3817(2)	90(1)	35(1)	C(32)	8858(3)	5299(2)	-2811(2)	62(1)
C(6)	7709(2)	3699(2)	876(1)	36(1)	C(33)	5635(2)	2286(2)	-686(1)	41(1)
C(7)	6972(2)	4863(2)	-703(1)	41(1)	C(34)	4957(2)	2199(2)	-1345(2)	45(1)
C(8)	5822(2)	4256(2)	-1429(1)	41(1)	C(35)	5067(3)	1077(2)	-1368(2)	63(1)
C(9)	6012(2)	3130(2)	-688(1)	37(1)	C(36)	4421(3)	920(3)	-1927(2)	79(1)
C(10)	8719(2)	1107(2)	3649(1)	35(1)	C(37)	3644(3)	1877(3)	-2477(2)	80(1)
C(11)	8463(2)	965(2)	4740(1)	39(1)	C(38)	3522(3)	2993(3)	-2472(2)	72(1)
C(12)	6445(2)	2012(2)	4331(1)	31(1)	C(39)	4167(2)	3162(2)	-1912(2)	55(1)
C(13)	5933(2)	1016(2)	4681(1)	35(1)	C(40)	9551(2)	5(2)	3233(2)	41(1)
C(14)	4234(2)	2760(2)	4707(1)	37(1)	C(41)	9489(2)	-1090(2)	3643(2)	52(1)
C(15)	5233(2)	3111(2)	4356(1)	33(1)	C(42)	10262(3)	-2072(2)	3226(2)	68(1)
C(16)	4996(2)	4300(2)	4182(2)	42(1)	C(43)	11098(3)	-1977(3)	2396(2)	77(1)
C(17)	3757(2)	5106(2)	4346(2)	53(1)	C(44)	11167(3)	-908(3)	1989(2)	80(1)
C(18)	2790(2)	4733(2)	4682(2)	54(1)	C(45)	10409(2)	82(2)	2403(2)	60(1)
C(19)	3007(2)	3547(2)	4874(2)	48(1)	C(46)	6734(2)	1767(2)	5994(1)	49(1)

In conclusion, a facile and efficient synthesis of a new class dispiro[oxindole-fused pyrimidine]pyrrolidine ring systems has been demonstrated by the highly regioselective cycloaddition reaction of compounds **1a-f** with

Table 2

Bond Lengths (Å) for Compound **4a**

S(1)-C(3)	1.7481(19)	C(4)-C(9)	1.470(3)	C(24)-C(25)	1.388(4)
S(1)-C(1)	1.8288(18)	C(5)-C(7)	1.490(3)	C(26)-C(27)	1.512(3)
N(1)-C(2)	1.372(2)	C(5)-C(6)	1.501(3)	C(27)-C(28)	1.380(3)
N(1)-C(3)	1.385(2)	C(6)-C(20)	1.521(3)	C(27)-C(32)	1.381(3)
N(1)-C(6)	1.479(2)	C(8)-C(9)	1.508(3)	C(28)-C(29)	1.411(5)
N(2)-C(3)	1.273(2)	C(9)-C(33)	1.339(3)	C(29)-C(30)	1.351(5)
N(2)-C(4)	1.428(2)	C(10)-C(40)	1.507(3)	C(30)-C(31)	1.350(4)
N(3)-C(7)	1.451(2)	C(10)-C(11)	1.518(3)	C(31)-C(32)	1.382(4)
N(3)-C(8)	1.459(3)	C(12)-C(15)	1.518(3)	C(33)-C(34)	1.477(3)
N(3)-C(26)	1.463(2)	C(12)-C(13)	1.554(3)	C(34)-C(35)	1.390(3)
N(4)-C(11)	1.456(2)	C(14)-C(19)	1.377(3)	C(34)-C(39)	1.392(3)
N(4)-C(46)	1.464(2)	C(14)-C(15)	1.389(3)	C(35)-C(36)	1.376(3)
N(4)-C(12)	1.468(2)	C(15)-C(16)	1.376(3)	C(36)-C(37)	1.368(4)
N(5)-C(13)	1.341(3)	C(16)-C(17)	1.394(3)	C(37)-C(38)	1.368(4)
N(5)-C(14)	1.404(3)	C(17)-C(18)	1.369(3)	C(38)-C(39)	1.385(3)
O(1)-C(2)	1.208(2)	C(18)-C(19)	1.377(3)	C(40)-C(45)	1.381(3)
O(2)-C(13)	1.228(2)	C(20)-C(25)	1.372(3)	C(40)-C(41)	1.386(3)
C(1)-C(2)	1.529(3)	C(20)-C(21)	1.380(3)	C(41)-C(42)	1.382(3)
C(1)-C(12)	1.567(3)	C(21)-C(22)	1.390(4)	C(42)-C(43)	1.370(4)
C(1)-C(10)	1.596(3)	C(22)-C(23)	1.364(5)	C(43)-C(44)	1.358(4)
C(4)-C(5)	1.336(3)	C(23)-C(24)	1.363(5)	C(44)-C(45)	1.385(4)

Table 3

Bond Angles (°) for Compound **4a**

C(3)-S(1)-C(1)	93.25(9)	C(5)-C(6)-C(20)	113.21(16)	C(20)-C(21)-C(22)	119.8(3)
C(2)-N(1)-C(3)	117.45(15)	N(3)-C(7)-C(5)	112.13(17)	C(23)-C(22)-C(21)	120.4(3)
C(2)-N(1)-C(6)	122.58(15)	N(3)-C(8)-C(9)	113.55(16)	C(24)-C(23)-C(22)	120.3(3)
C(3)-N(1)-C(6)	119.29(15)	C(33)-C(9)-C(4)	119.93(19)	C(23)-C(24)-C(25)	119.6(3)
C(3)-N(2)-C(4)	115.30(16)	C(33)-C(9)-C(8)	125.32(18)	C(20)-C(25)-C(24)	120.9(3)
C(7)-N(3)-C(8)	112.61(15)	C(4)-C(9)-C(8)	114.73(17)	N(3)-C(26)-C(27)	113.54(18)
C(7)-N(3)-C(26)	109.51(16)	C(40)-C(10)-C(11)	116.86(17)	C(28)-C(27)-C(32)	117.6(3)
C(8)-N(3)-C(26)	110.42(16)	C(40)-C(10)-C(1)	115.74(15)	C(28)-C(27)-C(26)	120.8(2)
C(11)-N(4)-C(46)	112.35(16)	C(11)-C(10)-C(1)	104.16(15)	C(32)-C(27)-C(26)	121.5(2)
C(11)-N(4)-C(12)	107.32(15)	N(4)-C(11)-C(10)	105.13(15)	C(27)-C(28)-C(29)	120.0(3)
C(46)-N(4)-C(12)	114.72(16)	N(4)-C(12)-C(15)	113.10(15)	C(30)-C(29)-C(28)	120.4(3)
C(13)-N(5)-C(14)	111.59(17)	N(4)-C(12)-C(13)	112.10(15)	C(31)-C(30)-C(29)	120.1(3)
C(2)-C(1)-C(12)	114.54(15)	C(15)-C(12)-C(13)	100.91(15)	C(30)-C(31)-C(32)	120.2(3)
C(2)-C(1)-C(10)	105.63(14)	N(4)-C(12)-C(1)	102.99(14)	C(27)-C(32)-C(31)	121.6(3)
C(12)-C(1)-C(10)	104.29(14)	C(15)-C(12)-C(1)	119.85(15)	C(9)-C(33)-C(34)	131.3(2)
C(2)-C(1)-S(1)	105.47(12)	C(13)-C(12)-C(1)	108.04(15)	C(35)-C(34)-C(39)	117.3(2)
C(12)-C(1)-S(1)	111.22(12)	O(2)-C(13)-N(5)	126.60(18)	C(35)-C(34)-C(33)	117.7(2)
C(10)-C(1)-S(1)	115.88(13)	O(2)-C(13)-C(12)	124.56(17)	C(39)-C(34)-C(33)	124.9(2)
O(1)-C(2)-N(1)	122.98(17)	N(5)-C(13)-C(12)	108.82(17)	C(36)-C(35)-C(34)	121.5(3)
O(1)-C(2)-C(1)	124.86(17)	C(19)-C(14)-C(15)	123.2(2)	C(37)-C(36)-C(35)	120.4(3)
N(1)-C(2)-C(1)	111.93(16)	C(19)-C(14)-N(5)	126.9(2)	C(36)-C(37)-C(38)	119.4(3)
N(2)-C(3)-N(1)	126.22(17)	C(15)-C(14)-N(5)	109.84(17)	C(37)-C(38)-C(39)	120.8(3)
N(2)-C(3)-S(1)	122.80(15)	C(16)-C(15)-C(14)	118.79(18)	C(38)-C(39)-C(34)	120.6(3)
N(1)-C(3)-S(1)	110.90(13)	C(16)-C(15)-C(12)	132.15(18)	C(45)-C(40)-C(41)	118.1(2)
C(5)-C(4)-N(2)	122.54(17)	C(14)-C(15)-C(12)	108.79(16)	C(45)-C(40)-C(10)	119.0(2)
C(5)-C(4)-C(9)	121.24(18)	C(15)-C(16)-C(17)	118.5(2)	C(41)-C(40)-C(10)	122.9(2)
N(2)-C(4)-C(9)	116.16(17)	C(18)-C(17)-C(16)	121.3(2)	C(42)-C(41)-C(40)	120.7(2)
C(4)-C(5)-C(7)	122.88(18)	C(17)-C(18)-C(19)	121.2(2)	C(43)-C(42)-C(41)	120.5(3)
C(4)-C(5)-C(6)	121.76(17)	C(18)-C(19)-C(14)	117.0(2)	C(44)-C(43)-C(42)	119.3(3)
C(7)-C(5)-C(6)	115.31(17)	C(25)-C(20)-C(21)	119.1(2)	C(43)-C(44)-C(45)	120.9(3)
N(1)-C(6)-C(5)	107.34(15)	C(25)-C(20)-C(6)	121.0(2)	C(40)-C(45)-C(44)	120.5(3)
N(1)-C(6)-C(20)	110.43(16)	C(21)-C(20)-C(6)	119.9(2)		

was 1.47-26.40°. A total of 10885 reflections were measured. *R* indices on all data was $R_1 = 0.0792$, $wR_2 = 0.1162$. Goodness of fit on F^2 was 1.018.

General Procedure for the Cycloaddition Reaction of 2-Arylmethylene-7-benzyl-9- (benzylidene)tetrahydropyrido[4,3-*d*]-thiazolo[3,2-*a*]pyrimidin-3-ones **1a-f** and the Azomethine Ylide Generated from Isatin **2** and Sarcosine **3**.

A mixture of 2-arylmethylene-7-benzyl-9-(benzylidene)tetrahydropyrido[4,3-*d*]thiazolo[3,2-*a*]pyrimidin-3-ones **1a-f** (0.5 mmol), isatin **2** (0.6 mmol) and sarcosine **3** (0.6 mmol) was refluxed in acetonitrile (100 ml). After completion of the reaction (monitored by TLC), the solvent was removed under reduced pressure and the residue was chromatographed on silica gel using petroleum ether-ethyl acetate (5:1) as eluent to give **4a-f**.

1-*N*-Methyl-spiro[2.3']oxindole-spiro[3.2"]7"-benzyl-9"-benzylidene-5"-phenyl-2", 3",6",7",8",9"-hexahydro-5"*H*-pyrido-[4,3-*d*]thiazolo[3,2-*a*]pyrimidin-3"-one-4-phenyl-pyrrolidine **4a**.

Compound **4a** was obtained as colorless soild, in 0.53 g, 73% yield, mp 210-211°; IR (KBr): 1363 (CH_3), 1700, 1721 (C=O), 3421 (N-H)cm^{-1}; ^{1}H NMR: δ 2.21 (s, 3H, -CH_3), 2.73 (d, *J* = 17.0 Hz, 1H, Pyridine-H), 3.05 (d, *J* = 17.0 Hz, 1H, Pyridine-H), 3.33 (d, *J* = 14.0 Hz, 1H, Pyridine-H), 3.35 (d, *J* = 12.5 Hz, 1H, Benzyl-H), 3.42-3.45 (m, 1H, H_d), 3.46 (d, *J* = 12.5 Hz, 1H, Benzyl-H), 3.74 (d, *J* = 14.0 Hz, 1H, Pyridine-H), 4.03-4.07 (m, 1H, H_e), 4.13-4.17 (m, 1H, H_c), 5.52 (s, 1H, H_a), 6.82-7.46 (m, 25H, Phenyl-H and H_b), 7.89 (bs, 1H, NH); ^{13}C NMR: 35.42, 52.58, 52.88, 55.01, 57.85, 58.60, 61.10, 70.68, 79.84, 110.24, 114.25, 123.62, 124.42, 125.86, 126.85, 127.36, 127.93, 128.05, 128.26, 128.28, 128.40, 128.79, 129.04, 129.34, 130.53, 130.56, 130.73, 133.59, 137.31, 137.44, 137.71, 139.40, 142.62, 152.50, 174.54, 177.13; MS *m/z*: 725 (M^+).

Anal. Calcd. for $C_{46}H_{39}N_5O_2S$: C, 76.11; H, 5.42; N, 9.65. Found: C, 76.14; H, 5.41; N, 9.63.

1-*N*-Methyl-spiro[2.3']oxindole-spiro[3.2"]7"-benzyl-9"-benzylidene-5"-phenyl-2", 3",6",7",8",9"-hexahydro-5"*H*-pyrido-[4,3-*d*]thiazolo[3,2-*a*]pyrimidin-3"-one-4-(4'-dimethyamino)-phenyl-pyrrolidine **4b**.

Compound **4b** was obtained as yellow solid, in 0.58 g, 75% yield, mp 201-201°; IR (KBr): 1368 (CH_3), 1720 (C=O), 3420 (N-H) cm^{-1}; ^{1}H NMR: δ 2.20 (s, 3H, -CH_3), 2.72 (d, *J* = 17.0 Hz, 1H, Pyridine-H), 2.96 (s, 6H, -$(CH_3)_2$), 3.04 (d, *J* = 17.0 Hz, 1H, Pyridine-H), 3.32 (d, *J* = 13.0 Hz, 1H, Benzyl-H), 3.37 (d, *J* = 14.5 Hz, 1H, Pyridine-H), 3.39 (dd, *J* = 7.5, 9.0 Hz, 1H, H_d), 3.45 (d, *J* = 13.0 Hz, 1H, Benzyl-H), 3.74 (d, *J* = 14.5 Hz, 1H, Pyridine-H), 3.95-3.99 (m, 1H, H_e), 4.05 (dd, *J* = 7.5, 10.5 Hz, 1H, H_c), 5.18 (s, 1H, H_a), 6.59-7.46 (m, 25H, Phenyl-H, H_b and NH); ^{13}C NMR: 35.23, 40.50, 52.42, 52.71, 54.36, 57.86, 58.36, 60.91, 71.30, 79.55, 109.84, 112.45, 113.99, 123.33, 124.46, 124.81, 125.55, 126.60, 127.13, 127.80, 128.04, 128.12, 128.19, 128.70, 128.79, 129.14, 130.37, 130.44, 131.05, 133.31, 137.20, 137.56, 139.37, 142.26, 150.01, 152.71, 174.54, 176.69; MS *m/z*: 768 (M^+).

Anal. Calcd. for $C_{48}H_{44}N_6O_2S$: C, 74.97; H, 5.77; N, 10.93. Found: C, 75.03; H, 5.79; N, 10.93.

1-*N*-Methyl-spiro[2.3']oxindole-spiro[3.2"]7"-benzyl-9"-benzylidene-5"-phenyl-2", 3",6",7",8",9"-hexahydro-5"*H*-pyrido-[4,3-*d*]thiazolo[3,2-*a*]pyrimidin-3"-one-4-(4'-methoxy)phenyl-pyrrolidine **4c**.

Compound **4c** was obtained as colorless solid, in 0.54 g, 71% yield, mp 172-173°; IR (KBr): 1370 (CH_3), 1721 (C=O), 3389 (N-H) cm^{-1}; ^{1}H NMR: δ 2.19 (s, 3H, -CH_3), 2.72 (d, *J* = 17.0 Hz, 1H, Pyridine-H), 3.04 (d, *J* = 17.0 Hz, 1H, Pyridine-H), 3.33 (d, *J* = 14.5 Hz, 1H, Pyridine-H), 3.34 (d, *J* = 13.0 Hz, 1H, Benzyl-H), 3.40 (dd, *J* = 8.0, 9.0 Hz, 1H, H_d), 3.45 (d, *J* = 13.0 Hz, 1H, Benzyl-H), 3.73 (d, *J* = 14.5 Hz, 1H, Pyridine-H), 3.81 (s, 3H, -OCH_3), 3.95-3.99 (m, 1H, H_e), 4.08 (dd, *J* = 8.0, 10.5 Hz, 1H, H_c), 5.19 (s, 1H, H_a), 6.76-7.46 (m, 24H, Phenyl-H and H_b), 7.67 (bs, 1H, NH); ^{13}C NMR: 35.20, 52.39, 52.68, 54.28, 55.22, 57.83, 58.34, 60.91, 70.82, 79.54, 109.97, 113.96, 114.01, 123.42, 124.28, 125.65, 126.64, 127.15, 127.86, 128.05, 128.11, 128.19, 128.82, 129.14, 129.30, 130.34, 130.47, 131.42, 133.41, 137.12, 137.50, 139.23, 142.32, 152.41, 159.10, 174.40, 176.84; MS *m/z*: 755 (M^+).

Anal. Calcd. for $C_{47}H_{41}N_5O_3S$: C, 74.68; H, 5.47; N, 9.26. Found: C, 74.70; H, 5.47; N, 9.25.

1-*N*-Methyl-spiro[2.3']oxindole-spiro[3.2"]7"-benzyl-9"-benzylidene-5"-phenyl-2", 3",6",7",8",9"-hexahydro-5"*H*-pyrido-[4,3-*d*]thiazolo[3,2-*a*]pyrimidin-3"-one-4-(4'- chloro)phenyl-pyrrolidine **4d**.

Compound **4d** was obtained as colorless solid, in 0.61 g, 80% yield, mp 190-191°; IR (KBr): 1368 (CH_3), 1711, 1720 (C=O), 3270 (N-H) cm^{-1}; ^{1}H NMR: δ 2.19 (s, 3H, -CH_3), 2.72 (d, *J* = 17.0 Hz, 1H, Pyridine-H), 3.04 (d, *J* = 17.0 Hz, 1H, Pyridine-H), 3.34 (d, *J* = 14.5 Hz, 1H, Pyridine-H), 3.34 (d, *J* = 13.0 Hz, 1H, Benzyl-H), 3.41 (dd, *J* = 7.5, 9.0 Hz, 1H, H_d), 3.46 (d, *J* = 13.0 Hz, 1H, Benzyl-H), 3.74 (d, *J* = 14.5 Hz, 1H, Pyridine-H), 3.94-3.98 (m, 1H, H_e), 4.07 (dd, *J* = 7.5, 10.0 Hz, 1H, H_c), 5.20 (s, 1H, H_a), 6.81-7.45 (m, 24H, Phenyl-H and H_b), 7.83 (bs, 1H, NH); ^{13}C NMR: 35.17, 52.39, 52.69, 54.25, 57.63, 58.38, 60.92, 70.20, 79.50, 110.07, 114.06, 123.52, 124.02, 125.78, 126.68, 127.16, 127.90, 128.07, 128.10, 128.20, 128.74, 128.88, 128.93, 129.12, 129.14, 130.25, 130.62, 131.68, 133.54, 133.67, 135.75, 137.08, 137.49, 139.13, 142.36, 151.93, 174.16, 176.79; MS *m/z*: 759 (M^+).

Anal. Calcd. for $C_{46}H_{38}ClN_5O_2S$: C, 72.66; H, 5.04; N, 9.21. Found: C, 72.65; H, 5.06; N, 9.24.

1-*N*-Methyl-spiro[2.3']oxindole-spiro[3.2"]7"-benzyl-9"-benzylidene-5"-phenyl-2", 3",6",7",8",9"-hexahydro-5"*H*-pyrido-[4,3-*d*]thiazolo[3,2-*a*]pyrimidin-3"-one-4-(2',4'-dichloro)phenyl-pyrrolidine **4e**.

Compound **4e** was obtained as colorless soild, in 0.67 g, 84% yield, mp 205-206°; IR (KBr): 1373 (CH_3) , 1708, 1724 (C=O), 3332 (N-H)cm^{-1}; ^{1}H NMR: δ 2.18 (s, 3H, -CH_3), 2.69 (d, *J* = 17.0 Hz, 1H, Pyridine-H), 2.96 (d, *J* = 17.0 Hz, 1H, Pyridine-H), 3.36 (d, *J* = 13.0 Hz, 1H, Benzyl-H), 3.38 (d, *J* = 14.0 Hz, 1H, Pyridine-H), 3.44 (d, *J* = 13.0 Hz, 1H, Benzyl-H), 3.46(dd, *J* = 8.5, 9.0 Hz, 1H, H_d), 3.70 (d, *J* = 14.0 Hz, 1H, Pyridine-H), 4.00-4.04 (m, 1H, H_e), 4.62-4.66 (m, 1H, H_c), 5.18 (s, 1H, H_a), 6.76-7.86 (m, 24H, Phenyl-H, H_b and NH); ^{13}C NMR: 35.40, 46.65, 52.40, 52.65, 56.37, 58.58, 60.86, 68.87, 80.17, 110.38, 114.01, 123.39, 123.44, 125.71, 126.66, 126.90, 127.15, 127.21, 128.05, 128.19, 128.60, 128.85, 128.87, 129.05, 129.11, 129.14, 130.18, 130.89, 131.63, 133.58, 133.93, 134.37, 136.94, 137.01, 137.10, 137.49, 142.44, 151.72, 173.61, 176.57; MS *m/z*: 793 (M^+).

Anal. Calcd. for $C_{46}H_{37}Cl_2N_5O_2S$: C, 69.51; H, 4.69; N, 8.81. Found: C, 69.55; H, 4.70; N, 8.81.

1-*N*-Methyl-spiro[2.3']oxindole-spiro[3.2"]7"-benzyl-9"-benzylidene-5"-phenyl-2", 3",6",7",8",9"-hexahydro-5"*H*-pyrido-[4,3-*d*]thiazolo[3,2-*a*]pyrimidin-3"-one-4-(2'-nitro)phenyl-pyrrolidine **4f**.

Compound **4f** was obtained as colorless soild, in 0.67 g, 87% yield, mp 205-206°; IR (KBr): 1348 (NO_2), 1372 (CH_3), 1528 (NO_2), 1707, 1724 (C=O), 3320 (N-H) cm^{-1}; ^1H NMR: δ 2.18 (s, 3H, -CH_3), 2.67 (d, J = 17.0 Hz, 1H, Pyridine-H), 2.92 (d, J = 17.0 Hz, 1H, Pyridine-H), 3.34 (d, J = 13.0 Hz, 1H, Benzyl-H), 3.36 (d, J = 14.0 Hz, 1H, Pyridine-H), 3.41 (d, J = 13.0 Hz, 1H, Benzyl-H), 3.48 (dd, J = 8.5, 9.0 Hz, 1H, H_d), 3.69 (d, J = 14.0 Hz, 1H, Pyridine-H), 4.00-4.04 (m, 1H, H_e), 4.67-4.71 (m, 1H, H_c), 5.09 (s, 1H, H_a), 6.79-8.35 (m, 24H, Phenyl-H and H_b) , 7.57 (bs, 1H, NH); ^{13}C NMR: 35.29, 45.27, 52.30, 52.60, 58.65, 58.95, 60.68, 69.51, 80.39, 110.31, 114.52, 123.23, 123.68, 124.12, 125.39, 126.58, 127.11, 128.02, 128.16, 128.37, 128.55, 128.74, 129.09, 129.12, 130.27, 130.86, 132.44, 132.90, 132.97, 137.15, 137.58, 137.79, 142.21, 150.99, 151.67, 173.14, 176.68; MS *m*/*z*: 770 (M^+).

Anal. Calcd. for $C_{46}H_{38}N_6O_4S$: C, 71.67; H, 4.97; N, 10.90. Found: C, 71.69; H, 4.97; N, 10.89.

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