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Synthesis and Characterization of 5'-benzylidene-1-(2-(1,3-dioxoisoindine-2-yloxy)ethyl)-3'-(5-phenyl-1,3,4-thiadiazole-2yl)spiro[indoline-3,2'thiazolidine]-2,4'-dione and Its Related Derivatives

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ABSTRACT

*Facile synthesis of **3** has been achieved by the cycloaddition reaction of mercapto acetic acid with Schiff base **2**, which in turn was prepared by the condensation reaction of substituted thaidiazole **1** with isatin. Condensation of **3** with substituted araldehydes afforded corresponding chalcones **4a-d**. Subsequent treatment of **4a-d** with bromoethoxyphthalimide to obtain final compounds **5a-d**. Structure confirmation was accomplished by spectral studies (IR, ^{1}H NMR) and elemental analysis of all the synthesized compounds.*

Keywords: Bromoethoxyphthalimide; chalcone; isatin; Schiff base; thiadiazole.

INTRODUCTION

During last few years there have been intense investigation of different classes of thaidiazole compounds, many of which known to possess important biological properties such as antimicrobial, [1] anticancer, [2] antitubercular, [3] anti-inflammatory, [4] analgesic, [5] anticonvulsant, [6] antihypertensive, [7] antioxidant, [8] antifungal [9] and antidepressant [10] activity. The chemistry of thiazolidin-4-one ring systems is of considerable interest as it is a core structure in various synthetic pharmaceuticals displaying a broad spectrum of biological activities such as anti-inflammatory, [11] antitubercular, [12] antibacterial, [13] antihistaminic, [14] antifungal, [15] antiHIV, [16] anticonvulsant [17] and cardiovascular [18] etc. Indole and Isatin containing compounds have been reported to possess a wide variety of biological properties *viz* anticancer, [19] antioxidant, [20] anti-inflammatory, [21] anticonvulsant, [22] antimalarial, [23] antipyretic, [24] antimicrobial, [25] antifungal, [26] analgesic, [27] antitubercular [28] etc. Diverse biological activities like anticonvulsant, [29] anticancer, [30] diuretic, [31] fungicidal and trypanocidal etc. have been observed for alkoxyphthalimide and related functionalities. The ability to inhibit growth of malarial parasite Plasmodium falsiparum [32] have also been observed for several aminoxy and related derivatives. Heterocyclic rings attached to alkoxyphthalimide group have been synthesized [33] by the previous group of workers and tested for various antimicrobial, antimalarial [34] and other activities. In view of above facts it was thought worthwhile to synthesize new structural entities incorporating above

pharmacophore in a single molecular framework using various heterocycles and alkoxyphthalimide moiety as individual building blocks with the hope to achieve enhanced biological activity.

MATERIALS AND METHODS

Melting points were determined by electro thermal method in open capillary tubes and are therefore uncorrected. Purity of the synthesized compounds was checked on silica gel G TLC plates of 2 mm thickness using ethyl acetate-chloroform as eluent system. The visualization of spot was carried out in an iodine chamber. The IR spectra of the compounds were recorded on a 4000-450 cm^{-1} ranges using KBr discs on FTIR IR RX1Perkin Elmer spectrophotometer and ^1H NMR were recorded on a Bruker DRX-200 MHz spectrometer in ($CDCl_3$) solvent using TMS as an internal standard. Bromoethoxyphthalimide bromide was prepared by reported method [35]. Structures of all the synthesized compounds were assigned on basis of their chemical tests as well as analytical and spectral data.

Synthesis of 5-phenyl-1,3,4-thiadiazole-2-amine (1): A mixture of thiosemicarbazide (0.91 g, 0.01 mol), benzoic acid (1.22g, 0.01 mol), and conc. sulphuric acid (5 mL) in 50 mL of ethanol was refluxed for 1.5 h and cold filtrate was poured onto crushed ice. The solid separated out was filtered, washed with cold water and recrystalized from ethanol. IR (KBr, cm^{-1}): 3060 (Ar C-H str.), 1313 (C-N str.), 1432 (C=N str.), 654 (C-S-C str.), 3380 (N-H str.); ^1H NMR ($CDCl_3$, δ): 7.2-7.9 (m, 5H, Ar-H), 6.34 (s, 2H, C-NH_2).

Synthesis of 3-(5-phenyl-1, 3, 4-thiadiazole-2-ylamino)indolin-2-one) (2): An equimolar mixture of **1** (0.01 mol, 1.17 g) and isatin (0.01 mol, 1.47 g) were refluxed in methanol (40 mL) in presence of catalytic amount of glacial acetic acid for 5 h. The solvent was removed by distillation under reduced pressure. Schiff base thus obtained was filtered and recrystallized from methanol. IR (KBr, cm^{-1}): 3120 (Ar C-H str.), 1385 (C-N str.), 1514 (C=N str.), 689 (C-S-C str.), 1715 (-C=O str.), 3442 (N-H str.); ^1H NMR ($CDCl_3$, δ): 7.09-8.10 (m, 9H, Ar-H), 7.2 (s, 1H, -NH).

Synthesis of 3'-(5-phenyl-1,3,4-thiadiazole-2-yl)spiro[indoline-3,2'-thiazolidine]-2,4'-dione (3): A well stirred solution of **2** (0.01 mol, 3.06 g) in dry DMF containing pinch of anhydrous $ZnCl_2$ and thioglycolic acid (0.02 mol, 1.4 mL) was refluxed for 12 h. Excess of solvent was distilled off under reduced pressure and the residual concentrated reaction mixture was cooled and poured into ice cold water. The separated solid was filtered, washed and recrystallized from ethanol. IR (KBr, cm^{-1}): 3165 (Ar C-H str.), 1326 (C-N str.), 1584 (C=N str.), 702 (C-S-C str.), 1701 (-C=O str.), 3302 (N-H str.); ^1H NMR ($CDCl_3$,δ): 7.12-8.25 (m, 9H, Ar-H), 6.9 (s, 1H, -NH), 3.72 (s, 2H, CH_2CO).

Synthesis of 5'-benzylidene-3'-(5-phenyl-1,3,4-thiadiazole-2-yl)spiro[indoline-3,2'-thiazolidine]-2,4'-dione (4a): To a refluxing mixture of **3** (0.01 mol, 3.80 g) and sodium acetate (0.02 mol, 1.64 g) in glacial acetic acid, benzaldehyde (0.01 mol, 1.06 mL) was added and refluxing was continued for 16 h. After completion of reaction, ice cold water was added in installments and constant stirring to the reaction mixture to get crude product which was filtered, washed and recrystallized from ethanol.
Compounds **4b-d** was also prepared by similar method using appropriate quantity of compounds with minor change in reaction conditions.

5'-benzylidene-3'-(5-phenyl-1,3,4-thiadiazole-2-yl)spiro[indoline-3,2' thiazolidine]-2,4'-dione (4a): IR (KBr, cm^{-1}): 3068 (Ar C-H str.), 1267 (C-N str.), 1584 (C=N str.), 706 (C-S-C str.), 1693 (-C=O str.), 3200 (N-H str.); ^1H NMR ($CDCl_3$,δ): 6.93-8.50 (m, 14H, Ar-H), 7.8 (s, 1H, -NH), 7.13 (s, 1H, C=CH-Ar).

5'-(4-methoxybenzylidene)-3'-(5-phenyl-1,3,4-thiadiazol-2-yl)spiro[indoline-3,2' thiazolidine]-2,4'-dione (4b): IR (KBr, cm^{-1}): 3027 (Ar C-H str.), 1217 (C-N str.), 1545 (C=N str.), 676 (C-S-C str.), 1660 (-C=O str.), 3189 (N-H str.), 1065 (C-O-CH_3 str.); ^1H NMR ($CDCl_3$,δ): 6.85-8.22 (m, 13H, Ar-H), 7.3 (s, 1H, -NH), 6.93 (s, 1H, C=CH-Ar), 3.52 (s. 3H, OCH_3).

5'-(4-dimethylamino)benzylidene)-3'-(5-phenyl-1,3,4-thiadiazol-2-yl)spiro[indoline-3,2'thiazolidine]-2,4'-dione (4c): IR (KBr, cm^{-1}): 3002 (Ar C-H str.), 1201 (C-N str.), 1503 (C=N str.), 645 (C-S-C str.), 1645 (-C=O str.), 3129 (N-H str.); ^{1}H NMR ($CDCl_3$,δ): 6.39-8.10 (m, 13H, Ar-H), 6.72 (s, 1H, -NH), 6.33 (s, 1H, C=CH-Ar), 2.80 (s. 6H, $N(CH_3)_2$).

5'-(4-chlorobenzylidene)-3'-(5-phenyl-1,3,4-thiadiazol-2-yl)spiro[indoline-3,2'thiazolidine]-2,4'-dione (4d): IR (KBr, cm^{-1}): 3122 (Ar C-H str.), 1390 (C-N str.), 1575 (C=N str.), 721 (C-S-C str.), 1740 (-C=O str.), 3252 (N-H str.), 770 (C-Cl str.); ^{1}H NMR ($CDCl_3$,δ): 7.10-8.89 (m, 13H, Ar-H), 8.32 (s, 1H, -NH), 7.42 (s, 1H, C=CH-Ar).

Synthesis of 5'-benzylidene-1-(2-(1,3-dioxoisoindine-2-yloxy)ethyl)-3'-(5-phenyl-1,3,4-thiadiazole-2 yl)spiro[indoline-3,2'-thiazolidine]-2,4'-dione (5a): A mixture of **4a** (4.68 g, 0.01 mol) and bromoethoxyphthalimide (2.70 g, 0.01 mol) in absolute ethanol (15 mL) was refluxed for 16 h using pyridine (0.02 mol) as a base. It was concentrated by removing the solvent under reduced pressure and the resultant filtrate was poured into crushed ice to obtain solid product, which was filtered, dried and recrystallized from alcohol.

Compounds **5b-d** was also synthesized by similar method using appropriate reactants with required change in reflux time.

5'-benzylidene-1-(2-(1,3-dioxoisoindine-2-yloxy)ethyl)-3'-(5-phenyl-1,3,4-thiadiazole-2yl)spiro [indo line-3,2'-thiazolidine]-2,4'-dione (5a): IR (KBr, cm^{-1}): 3159 (Ar C-H str.), 1240 (C-N str.), 1500 (C=N str.), 694 (C-S-C str.), 1711 (-C=O str.), 1325 (N-O str.), 1048 (C-O str.); ^{1}H NMR ($CDCl_3$,δ): 7.12-8.33 (m, 18H, Ar-H), 4.1 (t, 2H, $-OCH_2$), 3.28 (t, 2H, N- CH_2), 7.30 (s, 1H, C=CH-Ar).

1-(2-(1,3-dioxoisoindine-2-yloxy)ethyl)-5'-(4-methoxybenzylidene)-3'-(5-phenyl -1,3,4-thiadiazole-2 yl)spiro[indoline-3,2'-thiazolidine]-2,4'-dion (5b): IR (KBr, cm^{-1}): 3108 (Ar C-H str.), 1222 (C-N str.), 1488 (C=N str.), 667 (C-S-C str.), 1690 (-C=O str.), 1305 (N-O str.), 1078 (C-OCH_3 str.); ^{1}H NMR ($CDCl_3$, δ): 7.01-8.12 (m, 17H, Ar-H), 3.94 (t, 2H, $-OCH_2$), 3.07 (t, 2H, N- CH_2), 7.15 (s, 1H, C=CH-Ar), 3.60 (s, 3H, OCH_3).

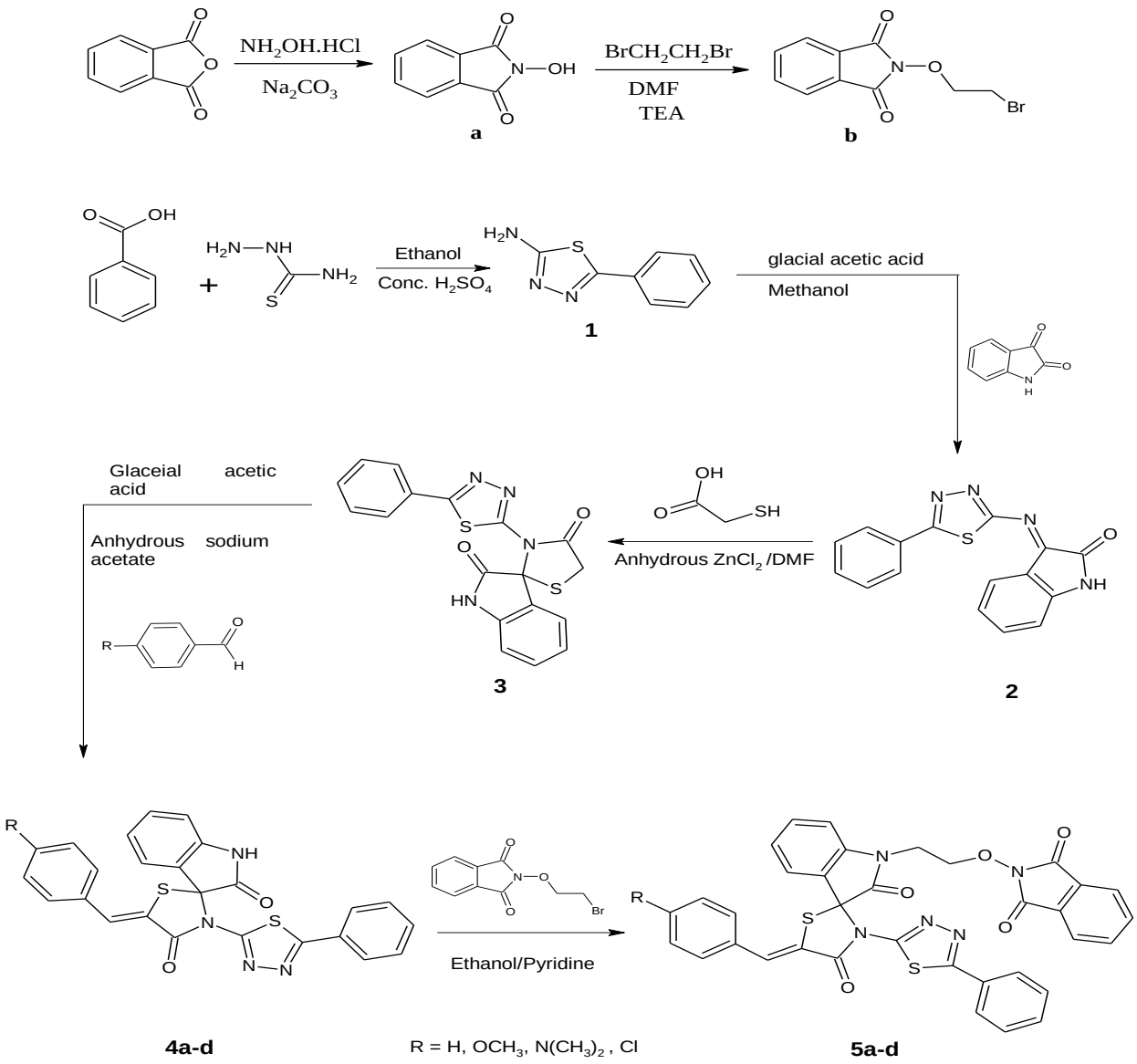
5'(4-(dimethylamino)benzylidene)-1-(2-(1,3-dioxoisoindine-2-yloxy)ethyl)-3'-(5-phenyl -1,3,4-thiadia zole-2 yl)spiro[indoline-3,2'-thiazolidine]-2,4'-dione (5c): IR (KBr, cm^{-1}): 3089 (Ar C-H str.), 1209 (C-N str.), 1462 (C=N str.), 709 (C-S-C str.), 1672 (-C=O str.), 1289 (N-O str.); ^{1}H NMR ($CDCl_3$,δ): 6.85-7.90 (m, 17H, Ar-H), 3.5 (t, 2H, $-OCH_2$), 2.9 (t, 2H, N- CH_2), 6.85 (s, 1H, C=CH-Ar), 2.55 (s, 6H, $N(CH_3)_2$).

5'(4-(chlorobenzylidene)-1-(2-(1,3-dioxoisoindine-2-yloxy)ethyl)-3'-(5-phenyl -1,3,4-thiadiazole-2 yl) spiro[indoline-3,2'-thiazolidine]-2,4'-dione (5d): IR (KBr, cm^{-1}): 3185 (Ar C-H str.), 1370 (C-N str.), 1620 (C=N str.), (C-S-C str.), 1722 (-C=O str.), 1360 (N-O str.), 798 (C-Cl str.); ^{1}HNMR ($CDCl_3$,δ): 7.34-8.76 (m, 17H, Ar-H), 4.32 (t, 2H, $-OCH_2$), 3.53 (t, 2H, N- CH_2), 7.6 (s, 1H, C=CH-Ar).

RESULTS AND DISCUSSION

5-phenyl-1,3,4-thiadiazole-2-amine **1** was prepared by refluxing benzoic acid with thiosemicarbazide in presence of conc. H_2SO_4. This was reacted with Isatin in methanolic media to furnish schiff base **2**. This gave a strong peak at 1715 cm^{-1} due to CO str. in IR. Cyclisation of **2** was carried out by refluxing it with thioglycolic acid/DMF followed by $ZnCl_2$ to give spiro compound **3**. Formation of compound **3** was confirmed by presence of C-S-C linkage at 702 cm^{-1} in IR and singlet at 3.72 δ for S-CH_2 in ^{1}H NMR. Treatment of spiro compound **3** with substituted araldehyde produced corresponding chalcone derivatives. Structures of compound **4a-d** was confirmed by disappearance of singlet at 3.72 for CH_2 and appearance of

new singlet for –C=CH-Ar at 7.13 in ^{1}H NMR spectrum. Subsequently, the NH proton of compound **4a-d** was replaced by bromoethoxyphthalimide moiety to yield final compounds **5a-d**. Structure of these compounds was confirmed by presence of C-O and N-O str. bands at 1048 and 1325 cm^{-1} respectively in IR spectrum and new signals in ^{1}H NMR spectrum at 3.28, triplet and 4.1, triplet for N-CH_2 and O-CH_2 respectively.



REACTION SCHEME

Table1. Physical and analytical data of synthesized compounds

	Mol. Formula	Mol. Weight	R	M.p. (^oC)	Yield (%)	Found (Calcd.) % N
1	$C_8H_7N_3S$	177	-	108	77	21.56 (23.71)
2	$C_{16}H_{10}N_4OS$	306	-	250	68	17.22(18.29)
3	$C_{18}H_{12}N_4O_2S_2$	380	-	290	63	11.67(14.73)
4a	$C_{25}H_{16}N_4O_2S_2$	468	H	320	58	9.99(11.96)
4b	$C_{26}H_{18}N_4O_3S_2$	498	OCH_3	302	65	10.34(11.24)
4c	$C_{27}H_{21}N_5O_2S_2$	511	$N(CH_3)_2$	333	54	12.22(13.69)
4d	$C_{25}H_{15}ClN_4O_2S_2$	502	Cl	347	66	10.78(11.14)
5a	$C_{35}H_{23}N_5O_5S_2$	657	H	180	51	8.96(10.65)
5b	$C_{36}H_{25}N_5O_6S_2$	687	OCH_3	210	53	9.12(10.18)
5c	$C_{37}H_{28}N_6O_5S_2$	700	$N(CH_3)_2$	196	66	10.76(11.99)
5d	$C_{35}H_{22}ClN_5O_5S_2$	692	Cl	222	71	9.56(10.12)

APPLICATIONS

The synthesized molecules contains for thiazolidinone, thaidiazole, isatin heterocyclic nuclei and a pharmacophore alkoxyphthalimide moiety. Apart from above entities the molecule is variously substituted with different substituent at different positions. Literature survey and different predictive software including PASS report and predict versatile important biological activities associated with synthesized molecule. Thiadiazole have been known to possess antiepileptic (against epileptic seizures), anti convulsant, antihypertensive, anti-inflammatory, antitubercular, analgesic, antidiabetic, antioxidant etc activities.Thiazoldine-4-one displays antitubercular, antihistaminic, anti HIV, cardiovascular, anti depre ssant and many other activities. Isatin have been reported to possess a vast number of activities mentioned above as well as antimalarial, antipyretic, antimicrobial activities. Alkoxyphthalimide and related functionalities have been claimed and reported to enhance various activities when present along with a molecule. Combination of all the four components given above may be important and significant in drug designing by rational and variation methods. Applicability of these molecules may be depicted by suitable linking of these parts can be stastiscally calculated by combinatorial libraries and justified by biological screening of the synthesized compounds.

CONCLUSIONS

In the present work synthesis of molecule no. (1-5a-d) was planned and carried out by exploring different methods. Compounds reported here are synthesized by the better methods of all the trials. The structure of compounds have been confirmed by elemental analysis and different spectral studies including IR, 1HNMR etc.

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